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(54) Title: IDENTIFICATION OF ESSENTIAL GENES IN MICROORGANISMS
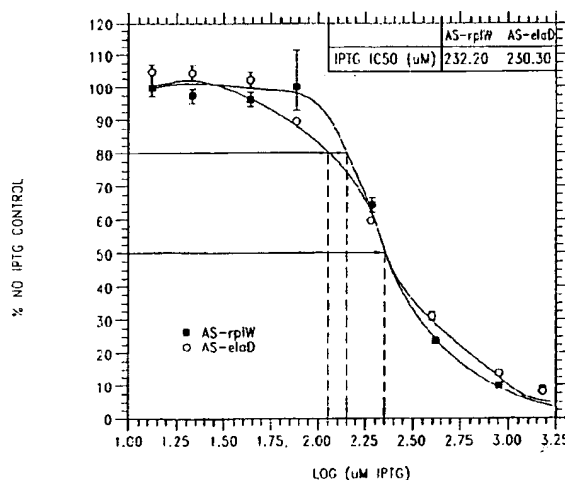
(57) Abstract: The sequences of antisense nucleic acids which inhibit the proliferation of prokaryotes are disclosed. Cell-based assays which employ the antisense nucleic acids to identify and develop antibiotics are also disclosed. The antisense nucleic acids can also be used to identify proteins required for proliferation, express these proteins or portions thereof, obtain antibodies capable of specifically binding to the expressed proteins, and to use those expressed proteins as a screen to isolate candidate molecules for rational drug discovery programs. The nucleic acids can also be used to screen for homologous nucleic acids that are required for proliferation in cells other than Staphylococcus aureus, Salmonella typhimurium, Klebsiella pneumoniae, and Pseudomonas aeruginosa. The nucleic acids of the present invention can also be used in various assay systems to screen for proliferation required genes in other organisms.

CH, CN, CO, CR, CU, CZ, CZ (utility model), DE, DE (utility model), DK, DK (utility model), DM, DZ, EC, EE, EE (utility model), ES, FI, FI (utility model), GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SK (utility model), SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW.

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IDENTIFICATION OF ESSENTIAL GENES IN MICROORGANISMS

Sequence Listing

The present application is being filed along with quadruplicate copies of a CD-ROM marked "Copy 1 - SEQUENCE LISTING PART," "Copy 2 - SEQUENCE LISTING PART,"

5 "Copy 3 - SEQUENCE LISTING PART," and "CRF" containing a Sequence Listing in electronic format. The quadruplicate copies of the CD-ROM each contain a file entitled 034VPC_final.ST25.txt, created on March 15, 2002, which is 181,323,311 bytes in size.

Background of the Invention

Since the discovery of penicillin, the use of antibiotics to treat the ravages of bacterial

10 infections has saved millions of lives. With the advent of these "miracle drugs," for a time it was popularly believed that humanity might, once and for all, be saved from the scourge of bacterial infections. In fact, during the 1980s and early 1990s, many large pharmaceutical companies cut back or eliminated antibiotics research and development. They believed that infectious disease caused by bacteria finally had been conquered and that markets for new drugs were limited.

15 Unfortunately, this belief was overly optimistic.

The tide is beginning to turn in favor of the bacteria as reports of drug resistant bacteria become more frequent. The United States Centers for Disease Control announced that one of the most powerful known antibiotics, vancomycin, was unable to treat an infection of the common *Staphylococcus aureus* (staph). This organism is commonly found in our environment and is

20 responsible for many nosocomial infections. The import of this announcement becomes clear when one considers that vancomycin was used for years to treat infections caused by *Staphylococcus* species as well as other stubborn strains of bacteria. In short, bacteria are becoming resistant to our most powerful antibiotics. If this trend continues, it is conceivable that we will return to a time when what are presently considered minor bacterial infections are fatal diseases.

25 Over-prescription and improper prescription habits by some physicians have caused an indiscriminate increase in the availability of antibiotics to the public. The patients are also partly responsible, since they will often improperly use the drug, thereby generating yet another population of bacteria that is resistant, in whole or in part, to traditional antibiotics.

The bacterial pathogens that have haunted humanity remain, in spite of the development of

30 modern scientific practices to deal with the diseases that they cause. Drug resistant bacteria are now an increasing threat to the health of humanity. A new generation of antibiotics is needed to once again deal with the pending health threat that bacteria present.

Discovery of New Antibiotics

As more and more bacterial strains become resistant to the panel of available antibiotics,

35 new antibiotics are required to treat infections. In the past, practitioners of pharmacology would have to rely upon traditional methods of drug discovery to generate novel, safe and efficacious compounds for the treatment of disease. Traditional drug discovery methods involve blindly testing potential drug candidate-molecules, often selected at random, in the hope that one might prove to be

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an effective treatment for some disease. The process is painstaking and laborious, with no guarantee of success. Today, the average cost to discover and develop a new drug exceeds US $500 million, an```d the average time from laboratory to patient is 15 years. Improving this process, even incrementally, would represent a huge advance in the generation of novel antimicrobial agents.

5   Newly emerging practices in drug discovery utilize a number of biochemical techniques to provide for directed approaches to creating new drugs, rather than discovering them at random. For example, gene sequences and proteins encoded thereby that are required for the proliferation of a cell or microorganism make excellent targets since exposure of bacteria to compounds active against these targets would result in the inactivation of the cell or microorganism. Once a target is 10   identified, biochemical analysis of that target can be used to discover or to design molecules that interact with and alter the functions of the target. Use of physical and computational techniques to analyze structural and biochemical properties of targets in order to derive compounds that interact with such targets is called rational drug design and offers great potential. Thus, emerging drug discovery practices use molecular modeling techniques, combinatorial chemistry approaches, and 15   other means to produce and screen and/or design large numbers of candidate compounds.

Nevertheless, while this approach to drug discovery is clearly the way of the future, problems remain. For example, the initial step of identifying molecular targets for investigation can be an extremely time consuming task. It may also be difficult to design molecules that interact with the target by using computer modeling techniques. Furthermore, in cases where the function of the 20   target is not known or is poorly understood, it may be difficult to design assays to detect molecules that interact with and alter the functions of the target. To improve the rate of novel drug discovery and development, methods of identifying important molecular targets in pathogenic cells or microorganisms and methods for identifying molecules that interact with and alter the functions of such molecular targets are urgently required.

25   *Escherichia coli* represents an excellent model system to understand bacterial biochemistry and physiology. The estimated 4288 genes scattered along the 4.6 x 10^6 base pairs of the *Escherichia coli* (*E. coli*) chromosome offer tremendous promise for the understanding of bacterial biochemical processes. In turn, this knowledge will assist in the development of new tools for the diagnosis and treatment of bacteria-caused human disease. The entire *E. coli* genome has been 30   sequenced, and this body of information holds a tremendous potential for application to the discovery and development of new antibiotic compounds. Yet, in spite of this accomplishment, the general functions or roles of many of these genes are still unknown. For example, the total number of proliferation-required genes contained within the E. coli genome is unknown, but has been variously estimated at around 200 to 700 (Armstrong, K.A. and Fan, D.P. Essential Genes in the 35   *metB-malB* Region of *Escherichia coli* K12, 1975, J. Bacteriol. 126: 48-55).

Staphylococcus aureus is a Gram positive microorganism which is the causative agent of many infectious diseases. Local infection by *Staphylococcus aureus* can cause abscesses on skin and cellulitis in subcutaneous tissues and can lead to toxin-related diseases such as toxic shock and

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scalded skin syndromes. *Staphylococcus aureus* can cause serious systemic infections such as osteomyelitis, endocarditis, pneumonia, and septicemia. *Staphylococcus aureus* is also a common cause of food poisoning, often arising from contact between prepared food and infected food industry workers. Antibiotic resistant strains of *Staphylococcus aureus* have recently been
5   identified, including those that are now resistant to all available antibiotics, thereby severely limiting the options of care available to physicians.

Pseudomonas aeruginosa is an important Gram negative opportunistic pathogen. It is the most common Gram negative found in nosocomial infections. *P. aeruginosa* is responsible for 16% of nosocomial pneumonia cases, 12% of hospital-acquired urinary tract infections, 8% of surgical
10 wound infections, and 10% of bloodstream infections. Immunocompromised patients, such as neutropenic cancer and bone marrow transplant patients, are particular susceptible to opportunistic infections. In this group of patients, *P. aeruginosa* is responsible for pneumonia and septicemia with attributable deaths reaching 30%. *P. aeruginosa* is also one of the most common and lethal pathogens responsible for ventilator-associated pneumonia in intubated patients, with directly
15 attributable death rates reaching 38%. Although *P. aeruginosa* outbreaks in burn patients are rare, it is associated with 60% death rates. In the AIDS population, *P. aeruginosa* is associated with 50% of deaths. Cystic fibrosis patients are characteristically susceptible to chronic infection by *P. aeruginosa*, which is responsible for high rates of illness and death. Current antibiotics work poorly for CF infections (Van Delden & Igelwski. 1998. Emerging Infectious Diseases 4:551-560;
20 references therein).

The gram negative enteric bacterial genus, *Salmonella*, encompasses at least 2 species. One of these, *S. enterica*, is divided into multiple subspecies and thousands of serotypes or serovars (Brenner, et al. 2000 J. Clin. Microbiol. 38:2465-2467). The *S. enterica* human pathogens include serovars Typhi, Paratyphi, Typhimurium, Cholerasuis, and many others deemed so closely related
25 that they are variants of a widespread species. Worldwide, disease in humans caused by *Salmonella* is a very serious problem. In many developing countries, *S. enterica* ser. Typhi still causes often-fatal typhoid fever. This problem has been reduced or eliminated in wealthy industrial states. However, enteritis induced by Salmonella is widespread and is the second most common disease caused by contaminated food in the United States (Edwards, BH 1999 "Salmonella and Shigella
30 species" Clin. Lab Med. 19(3):469-487). Though usually self-limiting in healthy individuals, others such as children, seniors, and those with compromising illnesses can be at much greater risk of serious illness and death.

Some *S. enterica* serovars (e.g. Typhimurium) cause a localized infection in the gastrointestinal tract. Other serovars (i.e. Typhi and Paratyphi) cause a much more serious systemic
35 infection. In animal models, these roles can be reversed which has allowed the use of the relatively safe *S. enterica* ser. Typhimurium as a surrogate in mice for the typhoid fever agent, *S. enterica* ser. Typhi. In mice, *S. enterica* ser Typhimurium causes a systemic infection similar in outcome to typhoid fever. Years of study of the *Salmonella* have led to the identification of many determinants

of virulence in animals and humans. *Salmonella* is interesting in its ability to localize to and invade the intestinal epithelium, induce morphologic changes in target cells via injection of certain cell-remodeling proteins, and to reside intracellularly in membrane-bound vesicles (Wallis, TS and Galyov, EE 2000 "Molecular basis of *Salmonella*-induced enteritis." Molec. Microb. 36:997-1005;

5   Falkow, S "The evolution of pathogenicity in Escherichia, Shigella, and Salmonella," Chap. 149 in Neidhardt, et al. eds pp 2723-2729; Gulig, PA "Pathogenesis of Systemic Disease," Chap. 152 in Neidhardt, et al. ppp 2774-2787). The immediate infection often results in a severe watery diarrhea but *Salmonella* also can establish and maintain a subclinical carrier state in some individuals. Spread is via food contaminated with sewage.

10   The gene products implicated in *Salmonella* pathogenesis include type three secretion systems (TTSS), proteins affecting cytoplasmic structure of the target cells, many proteins carrying out functions necessary for survival and proliferation of *Salmonella* in the host, as well as "traditional" factors such as endotoxin and secreted exotoxins. Additionally, there must be factors mediating species-specific illnesses. Despite this most of the genomes of *S. enterica* ser. Typhi (see

15   http://www.sanger.ac.uk/Projects/S_typhi/ for the genome database) and *S. enterica* ser. Typhimurium (see http://genome.wustl.edu/gsc/bacterial/salmonella.shtml for the genome database) are highly conserved and are mutually useful for gene identification in multiple serovars. The Salmonella are a complex group of enteric bacteria causing disease similar to but distinct from other gram negative enterics such as *E. coli* and have been a focus of biomedical research for the

20   last century.

Enterococcus faecalis, a Gram positive bacterium, is by far the most common member of the enterococci to cause infections in humans. *Enterococcus faecium* generally accounts for less than 20% of clinical isolates. Enterococci infections are mostly hospital-acquired though they are also associated with some community-acquired infections. Of nosocomial infections enterococci

25   account for 12% of bacteremia, 15% of surgical wound infections, 14% of urinary tract infections, and 5 to 15% of endocarditis cases (Huycke, M. M., D. F., Sahm and M. S. Gilmore. 1998. Emerging Infectious Diseases 4:239-249). Additionally enterococci are frequently associated with intraabdominal and pelvic infections. Enterococci infections are often hard to treat because they are resistant to a vast array of antimicrobial drugs, including aminoglycosides, penicillin, ampicillin

30   and vancomycin. The development of multiple-drug resistant (MDR) enterococci has made this bacteria a major concern for treating nosocomial infections.

Current drug discovery methods involve screening large number of prospective therapeutic compounds to identify those that are effective therapeutic agents or that can be optimized to provide an effective therapeutic agents. For example, the compounds to be evaluated for therapeutic

35   activity may be members of a library of compounds generated by combinatorial chemistry or members of a library of natural products.

Unfortunately, current methods are laborious and time consuming and may yield compounds which have already been identified or which act on gene products which are already

targeted by an existing therapeutic agent. In addition, a large number of compounds have been identified which have antimicrobial activity but which cannot be administered to individuals suffering from infection due to the fact that their targets are unknown.

The above reasons underscore the urgency of developing new antibiotics that are effective against *Escherichia coli, Staphylococcus aureus, Enterococcus faecalis, Klebsiella pneumoniae, Pseudomonas aeruginosa,* and *Salmonella typhimurium.* Accordingly, there is an urgent need for more novel methods to identify and characterize bacterial genomic sequences that encode gene products involved in proliferation, and are thereby potential new targets for antibiotic development. Likewise, there is a need for rapid screening techniques which yield novel compounds or compounds which act on novel targets as well as a need for methods which permit the identification of the target on which a compound with antimicrobial activity acts.

Prior to the present invention, the discovery of *Escherichia coli, Staphylococcus aureus, Enterococcus faecalis, Klebsiella pneumoniae, Pseudomonas aeruginosa,* and *Salmonella typhimurium* genes required for proliferation of the microorganism was a painstaking and slow process. Rapid screening techniques for identifying novel targets on which novel compounds act were undeveloped. While the detection and identification of new cellular drug targets within a *Escherichia coli, Staphylococcus aureus, Enterococcus faecalis, Klebsiella pneumoniae, Pseudomonas aeruginosa,* and *Salmonella typhimurium* cell is key for novel antibiotic development and effective treatment, the current methods of drug target discovery available prior to this invention have required painstaking processes requiring years of effort.

Summary of the Invention

Some aspects of the present invention are described in the numbered paragraphs below.

1.   A purified or isolated nucleic acid sequence comprising a nucleotide sequence consisting essentially of one of SEQ ID NOs: 1-6213, wherein expression of said nucleic acid inhibits proliferation of a cell.

2.   The nucleic acid sequence of Paragraph 1, wherein said nucleotide sequence is complementary to at least a portion of a coding sequence of a gene whose expression is required for proliferation of a cell.

3.   The nucleic acid of Paragraph 1, wherein said nucleic acid sequence is complementary to at least a portion of a nucleotide sequence of an RNA required for proliferation of a cell.

4.   The nucleic acid of Paragraph 3, wherein said RNA is an RNA comprising a sequence of nucleotides encoding more than one gene product.

5.   A purified or isolated nucleic acid comprising a fragment of one of SEQ ID NOs.: 1-6213, said fragment selected from the group consisting of fragments comprising at least 10, at least 20, at least 25, at least 30, at least 50 and more than 50 consecutive nucleotides of one of SEQ ID NOs: 1-6213.

6.   The fragment of Paragraph 5, wherein said fragment is included in a nucleic acid obtained from an organism selected from the group consisting of *Acinetobacter baumannii*, *Anaplasma marginale, Aspergillus fumigatus, Bacillus anthracis, Bacteroides fragilis, Bordetella pertussis, Borrelia burgdorferi, Burkholderia cepacia, Burkholderia fungorum, Burkholderia mallei, Campylobacter jejuni, Candida albicans, Candida glabrata* (also called *Torulopsis glabrata*), *Candida tropicalis, Candida parapsilosis, Candida guilliermondii, Candida krusei, Candida kefyr* (also called *Candida pseudotropicalis*), *Candida dubliniensis, Chlamydia pneumoniae, Chlamydia trachomatis, Clostridium acetobutylicum, Clostridium botulinum, Clostridium difficile, Clostridium perfringens, Coccidioides immitis, Corynebacterium diptheriae, Cryptococcus neoformans, Enterobacter cloacae, Enterococcus faecalis, Enterococcus faecium, Escherichia coli, Haemophilus influenzae, Helicobacter pylori, Histoplasma capsulatum, Klebsiella pneumoniae, Legionella pneumophila, Listeria monocytogenes, Moraxella catarrhalis, Mycobacterium avium, Mycobacterium bovis, Mycobacterium leprae, Mycobacterium tuberculosis, Mycoplasma genitalium, Mycoplasma pneumoniae, Neisseria gonorrhoeae, Neisseria meningitidis, Nocardia asteroides, Pasteurella haemolytica, Pasteurella multocida, Pneumocystis carinii, Proteus mirabilis, Proteus vulgaris, Pseudomonas aeruginosa, Pseudomonas putida, Pseudomonas syringae, Salmonella bongori, Salmonella cholerasuis, Salmonella enterica, Salmonella paratyphi, Salmonella typhi, Salmonella typhimurium, Shigella boydii, Shigella dysenteriae, Shigella flexneri, Shigella sonnei, Staphylococcus aureus, Staphylococcus epidermidis, Staphylococcus haemolyticus, Streptococcus pneumoniae, Streptococcus mutans, Streptococcus pyogenes, Treponema pallidum, Ureaplasma urealyticum, Vibrio cholerae, Vibrio parahaemolyticus, Vibrio vulnificans, Yersinia enterocolitica, Yersinia pestis* and any species falling within the genera of any of the above species.

7.   The fragment of Paragraph 5, wherein said fragment is included in a nucleic acid obtained from an organism other than *Escherichia coli*.

8.   A vector comprising a promoter operably linked to the nucleic acid of any one of Paragraphs 1-7.

9.   The vector of Paragraph 8, wherein said promoter is active in a microorganism selected from the group consisting of *Acinetobacter baumannii, Anaplasma marginale, Aspergillus fumigatus, Bacillus anthracis, Bacteroides fragilis, Bordetella pertussis, Borrelia burgdorferi, Burkholderia cepacia, Burkholderia fungorum, Burkholderia mallei, Campylobacter jejuni, Candida albicans, Candida glabrata* (also called *Torulopsis glabrata*), *Candida tropicalis, Candida parapsilosis, Candida guilliermondii, Candida krusei, Candida kefyr* (also called *Candida pseudotropicalis*), *Candida dubliniensis, Chlamydia pneumoniae, Chlamydia trachomatis, Clostridium acetobutylicum, Clostridium botulinum, Clostridium difficile, Clostridium perfringens, Coccidioides immitis, Corynebacterium diptheriae, Cryptococcus neoformans, Enterobacter cloacae, Enterococcus faecalis, Enterococcus faecium, Escherichia coli, Haemophilus influenzae, Helicobacter pylori, Histoplasma capsulatum, Klebsiella pneumoniae, Legionella pneumophila, Listeria monocytogenes, Moraxella catarrhalis, Mycobacterium avium, Mycobacterium bovis,*

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Mycobacterium leprae, Mycobacterium tuberculosis, Mycoplasma genitalium, Mycoplasma pneumoniae, Neisseria gonorrhoeae, Neisseria meningitidis, Nocardia asteroides, Pasteurella haemolytica, Pasteurella multocida, Pneumocystis carinii, Proteus mirabilis, Proteus vulgaris, Pseudomonas aeruginosa, Pseudomonas putida, Pseudomonas syringae, Salmonella bongori,

5   *Salmonella cholerasuis, Salmonella enterica, Salmonella paratyphi, Salmonella typhi, Salmonella typhimurium, Shigella boydii, Shigella dysenteriae, Shigella flexneri, Shigella sonnei, Staphylococcus aureus, Staphylococcus epidermidis, Staphylococcus haemolyticus, Streptococcus pneumoniae, Streptococcus mutans, Streptococcus pyogenes, Treponema pallidum, Ureaplasma urealyticum, Vibrio cholerae, Vibrio parahaemolyticus, Vibrio vulnificans, Yersinia enterocolitica,*

10   *Yersinia pestis* and any species falling within the genera of any of the above species.

10.   A host cell containing the vector of Paragraph 8 or Paragraph 9.

11.   A purified or isolated antisense nucleic acid comprising a nucleotide sequence complementary to at least a portion of an intragenic sequence, intergenic sequence, sequences spanning at least a portion of two or more genes, 5' noncoding region, or 3' noncoding region

15   within an operon comprising a proliferation-required gene whose activity or expression is inhibited by an antisense nucleic acid comprising the nucleotide sequence of one of SEQ ID NOs.: 1-6213.

12.   The purified or isolated antisense nucleic acid of Paragraph 11, wherein said antisense nucleic acid is complementary to a nucleic acid from an organism selected from the group consisting of *Acinetobacter baumannii, Anaplasma marginale, Aspergillus fumigatus, Bacillus*

20   *anthracis, Bacteroides fragilis, Bordetella pertussis, Borrelia burgdorferi, Burkholderia cepacia, Burkholderia fungorum, Burkholderia mallei, Campylobacter jejuni, Candida albicans, Candida glabrata* (also called *Torulopsis glabrata*), *Candida tropicalis, Candida parapsilosis, Candida guilliermondii, Candida krusei, Candida kefyr* (also called *Candida pseudotropicalis*), *Candida dubliniensis, Chlamydia pneumoniae, Chlamydia trachomatis, Clostridium acetobutylicum,*

25   *Clostridium botulinum, Clostridium difficile, Clostridium perfringens, Coccidioides immitis, Corynebacterium diptheriae, Cryptococcus neoformans, Enterobacter cloacae, Enterococcus faecalis, Enterococcus faecium, Escherichia coli, Haemophilus influenzae, Helicobacter pylori, Histoplasma capsulatum, Klebsiella pneumoniae, Legionella pneumophila, Listeria monocytogenes, Moraxella catarrhalis, Mycobacterium avium, Mycobacterium bovis,*

30   *Mycobacterium leprae, Mycobacterium tuberculosis, Mycoplasma genitalium, Mycoplasma pneumoniae, Neisseria gonorrhoeae, Neisseria meningitidis, Nocardia asteroides, Pasteurella haemolytica, Pasteurella multocida, Pneumocystis carinii, Proteus mirabilis, Proteus vulgaris, Pseudomonas aeruginosa, Pseudomonas putida, Pseudomonas syringae, Salmonella bongori, Salmonella cholerasuis, Salmonella enterica, Salmonella paratyphi, Salmonella typhi, Salmonella*

35   *typhimurium, Shigella boydii, Shigella dysenteriae, Shigella flexneri, Shigella sonnei, Staphylococcus aureus, Staphylococcus epidermidis, Staphylococcus haemolyticus, Streptococcus pneumoniae, Streptococcus mutans, Streptococcus pyogenes, Treponema pallidum, Ureaplasma*

urealyticum, Vibrio cholerae, Vibrio parahaemolyticus, Vibrio vulnificans, Yersinia enterocolitica, Yersinia pestis and any species falling within the genera of any of the above species.

13.　　The purified or isolated antisense nucleic acid of Paragraph 11, wherein said nucleotide sequence is complementary to a nucleotide sequence of a nucleic acid from an organism other than *E. coli.*

14.　　The purified or isolated antisense nucleic acid of Paragraph 11, wherein said proliferation-required gene comprises a nucleotide sequence selected from the group consisting of SEQ ID NOS.: 6214-42397.

15.　　A purified or isolated nucleic acid comprising a nucleotide sequence having at least 70% identity to a nucleotide sequence selected from the group consisting of SEQ ID NOs.: 1-6213, fragments comprising at least 25 consecutive nucleotides of SEQ ID NOs.: 1-6213, the nucleotide sequences complementary to SEQ ID NOs.: 1-6213 and the sequences complementary to fragments comprising at least 25 consecutive nucleotides of SEQ ID NOs.: 1-6213 as determined using BLASTN version 2.0 with the default parameters.

16.　　The purified or isolated nucleic acid of Paragraph 15, wherein said nucleic acid is obtained from an organism selected from the group consisting of *Acinetobacter baumannii, Anaplasma marginale, Aspergillus fumigatus, Bacillus anthracis, Bacteroides fragilis, Bordetella pertussis, Borrelia burgdorferi, Burkholderia cepacia, Burkholderia fungorum, Burkholderia mallei, Campylobacter jejuni, Candida albicans, Candida glabrata* (also called *Torulopsis glabrata), Candida tropicalis, Candida parapsilosis, Candida guilliermondii, Candida krusei, Candida kefyr* (also called *Candida pseudotropicalis), Candida dubliniensis, Chlamydia pneumoniae, Chlamydia trachomatis, Clostridium acetobutylicum, Clostridium botulinum, Clostridium difficile, Clostridium perfringens, Coccidioides immitis, Corynebacterium diptheriae, Cryptococcus neoformans, Enterobacter cloacae, Enterococcus faecalis, Enterococcus faecium, Escherichia coli, Haemophilus influenzae, Helicobacter pylori, Histoplasma capsulatum, Klebsiella pneumoniae, Legionella pneumophila, Listeria monocytogenes, Moraxella catarrhalis, Mycobacterium avium, Mycobacterium bovis, Mycobacterium leprae, Mycobacterium tuberculosis, Mycoplasma genitalium, Mycoplasma pneumoniae, Neisseria gonorrhoeae, Neisseria meningitidis, Nocardia asteroides, Pasteurella haemolytica, Pasteurella multocida, Pneumocystis carinii, Proteus mirabilis, Proteus vulgaris, Pseudomonas aeruginosa, Pseudomonas putida, Pseudomonas syringae, Salmonella bongori, Salmonella cholerasuis, Salmonella enterica, Salmonella paratyphi, Salmonella typhi, Salmonella typhimurium, Shigella boydii, Shigella dysenteriae, Shigella flexneri, Shigella sonnei, Staphylococcus aureus, Staphylococcus epidermidis, Staphylococcus haemolyticus, Streptococcus pneumoniae, Streptococcus mutans, Streptococcus pyogenes, Treponema pallidum, Ureaplasma urealyticum, Vibrio cholerae, Vibrio parahaemolyticus, Vibrio vulnificans, Yersinia enterocolitica, Yersinia pestis* and any species falling within the genera of any of the above species.

17.　　The nucleic acid of Paragraph 15, wherein said nucleic acid is obtained from an organism other than *E. coli.*

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18.   A vector comprising a promoter operably linked to a nucleic acid encoding a polypeptide whose expression is inhibited by an antisense nucleic acid comprising a nucleotide sequence of any one of SEQ ID NOs.: 1-6213.

19.   The vector of Paragraph 18, wherein said nucleic acid encoding said polypeptide is obtained from an organism selected from the group consisting of *Acinetobacter baumannii, Anaplasma marginale, Aspergillus fumigatus, Bacillus anthracis, Bacteroides fragilis, Bordetella pertussis, Borrelia burgdorferi, Burkholderia cepacia, Burkholderia fungorum, Burkholderia mallei, Campylobacter jejuni, Candida albicans, Candida glabrata* (also called *Torulopsis glabrata*), *Candida tropicalis, Candida parapsilosis, Candida guilliermondii, Candida krusei, Candida kefyr* (also called *Candida pseudotropicalis*), *Candida dubliniensis, Chlamydia pneumoniae, Chlamydia trachomatis, Clostridium acetobutylicum, Clostridium botulinum, Clostridium difficile, Clostridium perfringens, Coccidioides immitis, Corynebacterium diptheriae, Cryptococcus neoformans, Enterobacter cloacae, Enterococcus faecalis, Enterococcus faecium, Escherichia coli, Haemophilus influenzae, Helicobacter pylori, Histoplasma capsulatum, Klebsiella pneumoniae, Legionella pneumophila, Listeria monocytogenes, Moraxella catarrhalis, Mycobacterium avium, Mycobacterium bovis, Mycobacterium leprae, Mycobacterium tuberculosis, Mycoplasma genitalium, Mycoplasma pneumoniae, Neisseria gonorrhoeae, Neisseria meningitidis, Nocardia asteroides, Pasteurella haemolytica, Pasteurella multocida, Pneumocystis carinii, Proteus mirabilis, Proteus vulgaris, Pseudomonas aeruginosa, Pseudomonas putida, Pseudomonas syringae, Salmonella bongori, Salmonella cholerasuis, Salmonella enterica, Salmonella paratyphi, Salmonella typhi, Salmonella typhimurium, Shigella boydii, Shigella dysenteriae, Shigella flexneri, Shigella sonnei, Staphylococcus aureus, Staphylococcus epidermidis, Staphylococcus haemolyticus, Streptococcus pneumoniae, Streptococcus mutans, Streptococcus pyogenes, Treponema pallidum, Ureaplasma urealyticum, Vibrio cholerae, Vibrio parahaemolyticus, Vibrio vulnificans, Yersinia enterocolitica, Yersinia pestis* and any species falling within the genera of any of the above species.

20.   The vector of Paragraph 18, wherein said nucleotide sequence encoding said polypeptide is obtained from an organism other than *E. coli*.

21.   A host cell containing the vector of Paragraph 18.

22.   The vector of Paragraph 18, wherein said polypeptide comprises a polypeptide comprising an amino acid sequence selected from the group consisting of SEQ ID NOs: 42398-78581.

23.   The vector of Paragraph 18, wherein said promoter is operably linked to a nucleic acid comprising a nucleotide sequence selected from the group consisting of SEQ ID NOS.: 6214-42397.

24.   A purified or isolated polypeptide comprising a polypeptide whose expression is inhibited by an antisense nucleic acid comprising a nucleotide sequence of any one of SEQ ID NOs.: 1-6213, or a fragment selected from the group consisting of fragments comprising at least 5,

at least 10, at least 20, at least 30, at least 40, at least 50, at least 60 or more than 60 consecutive amino acids of one of the said polypeptides.

    25. The polypeptide of Paragraph 24, wherein said polypeptide comprises an amino acid sequence of any one of SEQ ID NOs.: 42398-78581 or a fragment comprising at least 5, at least 10, at least 20, at least 30, at least 40, at least 50, at least 60 or more than 60 consecutive amino acids of a polypeptide comprising an amino acid sequence selected from the group consisting of SEQ ID NOs.: 42398-78581.

    26. The polypeptide of Paragraph 24, wherein said polypeptide is obtained from an organism selected from the group consisting of *Acinetobacter baumannii, Anaplasma marginale, Aspergillus fumigatus, Bacillus anthracis, Bacteroides fragilis, Bordetella pertussis, Borrelia burgdorferi, Burkholderia cepacia, Burkholderia fungorum, Burkholderia mallei, Campylobacter jejuni, Candida albicans, Candida glabrata* (also called *Torulopsis glabrata*), *Candida tropicalis, Candida parapsilosis, Candida guilliermondii, Candida krusei, Candida kefyr* (also called *Candida pseudotropicalis*), *Candida dubliniensis, Chlamydia pneumoniae, Chlamydia trachomatis, Clostridium acetobutylicum, Clostridium botulinum, Clostridium difficile, Clostridium perfringens, Coccidioides immitis, Corynebacterium diptheriae, Cryptococcus neoformans, Enterobacter cloacae, Enterococcus faecalis, Enterococcus faecium, Escherichia coli, Haemophilus influenzae, Helicobacter pylori, Histoplasma capsulatum, Klebsiella pneumoniae, Legionella pneumophila, Listeria monocytogenes, Moraxella catarrhalis, Mycobacterium avium, Mycobacterium bovis, Mycobacterium leprae, Mycobacterium tuberculosis, Mycoplasma genitalium, Mycoplasma pneumoniae, Neisseria gonorrhoeae, Neisseria meningitidis, Nocardia asteroides, Pasteurella haemolytica, Pasteurella multocida, Pneumocystis carinii, Proteus mirabilis, Proteus vulgaris, Pseudomonas aeruginosa, Pseudomonas putida, Pseudomonas syringae, Salmonella bongori, Salmonella cholerasuis, Salmonella enterica, Salmonella paratyphi, Salmonella typhi, Salmonella typhimurium, Shigella boydii, Shigella dysenteriae, Shigella flexneri, Shigella sonnei, Staphylococcus aureus, Staphylococcus epidermidis, Staphylococcus haemolyticus, Streptococcus pneumoniae, Streptococcus mutans, Streptococcus pyogenes, Treponema pallidum, Ureaplasma urealyticum, Vibrio cholerae, Vibrio parahaemolyticus, Vibrio vulnificans, Yersinia enterocolitica, Yersinia pestis* and any species falling within the genera of any of the above species.

    27. The polypeptide of Paragraph 24, wherein said polypeptide is obtained from an organism other than *E. coli*.

    28. A purified or isolated polypeptide comprising a polypeptide having at least 25% amino acid identity to a polypeptide whose expression is inhibited by a nucleic acid comprising a nucleotide sequence selected from the group consisting of SEQ ID NOs.: 1-6213, or at least 25% amino acid identity to a fragment comprising at least 10, at least 20, at least 30, at least 40, at least 50, at least 60 or more than 60 consecutive amino acids of a polypeptide whose expression is inhibited by a nucleic acid comprising a nucleotide sequence selected from the group consisting of SEQ ID NOs.: 1-6213 as determined using FASTA version 3.0t78 with the default parameters.

29.   The polypeptide of Paragraph 28, wherein said polypeptide has at least 25% identity to a polypeptide comprising one of SEQ ID NOs: 42398-78581 or at least 25% identity to a fragment comprising at least 5, at least 10, at least 20, at least 30, at least 40, at least 50, at least 60 or more than 60 consecutive amino acids of a polypeptide comprising one of SEQ ID NOs.: 42398-78581 as determined using FASTA version 3.0t78 with the default parameters.

30.   The polypeptide of Paragraph 28, wherein said polypeptide is obtained from an organism selected from the group consisting of *Acinetobacter baumannii, Anaplasma marginale, Aspergillus fumigatus, Bacillus anthracis, Bacteroides fragilis, Bordetella pertussis, Borrelia burgdorferi, Burkholderia cepacia, Burkholderia fungorum, Burkholderia mallei, Campylobacter jejuni, Candida albicans, Candida glabrata* (also called *Torulopsis glabrata*), *Candida tropicalis, Candida parapsilosis, Candida guilliermondii, Candida krusei, Candida kefyr* (also called *Candida pseudotropicalis*), *Candida dubliniensis, Chlamydia pneumoniae, Chlamydia trachomatis, Clostridium acetobutylicum, Clostridium botulinum, Clostridium difficile, Clostridium perfringens, Coccidioides immitis, Corynebacterium diptheriae, Cryptococcus neoformans, Enterobacter cloacae, Enterococcus faecalis, Enterococcus faecium, Escherichia coli, Haemophilus influenzae, Helicobacter pylori, Histoplasma capsulatum, Klebsiella pneumoniae, Legionella pneumophila, Listeria monocytogenes, Moraxella catarrhalis, Mycobacterium avium, Mycobacterium bovis, Mycobacterium leprae, Mycobacterium tuberculosis, Mycoplasma genitalium, Mycoplasma pneumoniae, Neisseria gonorrhoeae, Neisseria meningitidis, Nocardia asteroides, Pasteurella haemolytica, Pasteurella multocida, Pneumocystis carinii, Proteus mirabilis, Proteus vulgaris, Pseudomonas aeruginosa, Pseudomonas putida, Pseudomonas syringae, Salmonella bongori, Salmonella cholerasuis, Salmonella enterica, Salmonella paratyphi, Salmonella typhi, Salmonella typhimurium, Shigella boydii, Shigella dysenteriae, Shigella flexneri, Shigella sonnei, Staphylococcus aureus, Staphylococcus epidermidis, Staphylococcus haemolyticus, Streptococcus pneumoniae, Streptococcus mutans, Streptococcus pyogenes, Treponema pallidum, Ureaplasma urealyticum, Vibrio cholerae, Vibrio parahaemolyticus, Vibrio vulnificans, Yersinia enterocolitica, Yersinia pestis* and any species falling within the genera of any of the above species.

31.   The polypeptide of Paragraph 28, wherein said polypeptide is obtained from an organism other than *E. coli*.

32.   An antibody capable of specifically binding the polypeptide of one of Paragraphs 28-31.

33.   A method of producing a polypeptide, comprising introducing a vector comprising a promoter operably linked to a nucleic acid comprising a nucleotide sequence encoding a polypeptide whose expression is inhibited by an antisense nucleic acid comprising one of SEQ ID NOs.: 1-6213 into a cell.

34.   The method of Paragraph 33, further comprising the step of isolating said polypeptide.

35. The method of Paragraph 33, wherein said polypeptide comprises an amino acid sequence selected from the group consisting of SEQ ID NOs.: 42398-78581.

36. The method of Paragraph 33, wherein said nucleic acid encoding said polypeptide is obtained from an organism selected from the group consisting of *Acinetobacter baumannii, Anaplasma marginale, Aspergillus fumigatus, Bacillus anthracis, Bacteroides fragilis, Bordetella pertussis, Borrelia burgdorferi, Burkholderia cepacia, Burkholderia fungorum, Burkholderia mallei, Campylobacter jejuni, Candida albicans, Candida glabrata* (also called *Torulopsis glabrata*), *Candida tropicalis, Candida parapsilosis, Candida guilliermondii, Candida krusei, Candida kefyr* (also called *Candida pseudotropicalis*), *Candida dubliniensis, Chlamydia pneumoniae, Chlamydia trachomatis, Clostridium acetobutylicum, Clostridium botulinum, Clostridium difficile, Clostridium perfringens, Coccidioides immitis, Corynebacterium diptheriae, Cryptococcus neoformans, Enterobacter cloacae, Enterococcus faecalis, Enterococcus faecium, Escherichia coli, Haemophilus influenzae, Helicobacter pylori, Histoplasma capsulatum, Klebsiella pneumoniae, Legionella pneumophila, Listeria monocytogenes, Moraxella catarrhalis, Mycobacterium avium, Mycobacterium bovis, Mycobacterium leprae, Mycobacterium tuberculosis, Mycoplasma genitalium, Mycoplasma pneumoniae, Neisseria gonorrhoeae, Neisseria meningitidis, Nocardia asteroides, Pasteurella haemolytica, Pasteurella multocida, Pneumocystis carinii, Proteus mirabilis, Proteus vulgaris, Pseudomonas aeruginosa, Pseudomonas putida, Pseudomonas syringae, Salmonella bongori, Salmonella cholerasuis, Salmonella enterica, Salmonella paratyphi, Salmonella typhi, Salmonella typhimurium, Shigella boydii, Shigella dysenteriae, Shigella flexneri, Shigella sonnei, Staphylococcus aureus, Staphylococcus epidermidis, Staphylococcus haemolyticus, Streptococcus pneumoniae, Streptococcus mutans, Streptococcus pyogenes, Treponema pallidum, Ureaplasma urealyticum, Vibrio cholerae, Vibrio parahaemolyticus, Vibrio vulnificans, Yersinia enterocolitica, Yersinia pestis* and any species falling within the genera of any of the above species.

37. The method of Paragraph 33, wherein said nucleic acid encoding said polypeptide is obtained from an organism other than *E. coli*.

38. The method of Paragraph 33, wherein said promoter is operably linked to a nucleic acid comprising a nucleotide sequence selected from the group consisting of SEQ ID NOS.: 6214-42397.

39. A method of inhibiting proliferation of a cell in an individual comprising inhibiting the activity or reducing the amount of a gene product whose expression is inhibited by an antisense nucleic acid comprising a nucleotide sequence selected from the group consisting of SEQ ID NOs.: 1-6213 or inhibiting the activity or reducing the amount of a nucleic acid encoding said gene product.

40. The method of Paragraph 39, wherein said method comprises inhibiting said activity or reducing said amount of a gene product in an organism selected from the group consisting of *Acinetobacter baumannii, Anaplasma marginale, Aspergillus fumigatus, Bacillus anthracis, Bacteroides fragilis, Bordetella pertussis, Borrelia burgdorferi, Burkholderia cepacia,*

Burkholderia fungorum, Burkholderia mallei, Campylobacter jejuni, Candida albicans, Candida glabrata (also called *Torulopsis glabrata*), *Candida tropicalis, Candida parapsilosis, Candida guilliermondii, Candida krusei, Candida kefyr* (also called *Candida pseudotropicalis*), *Candida dubliniensis, Chlamydia pneumoniae, Chlamydia trachomatis, Clostridium acetobutylicum,*

5 *Clostridium botulinum, Clostridium difficile, Clostridium perfringens, Coccidioides immitis, Corynebacterium diptheriae, Cryptococcus neoformans, Enterobacter cloacae, Enterococcus faecalis, Enterococcus faecium, Escherichia coli, Haemophilus influenzae, Helicobacter pylori, Histoplasma capsulatum, Klebsiella pneumoniae, Legionella pneumophila, Listeria monocytogenes, Moraxella catarrhalis, Mycobacterium avium, Mycobacterium bovis,*

10 *Mycobacterium leprae, Mycobacterium tuberculosis, Mycoplasma genitalium, Mycoplasma pneumoniae, Neisseria gonorrhoeae, Neisseria meningitidis, Nocardia asteroides, Pasteurella haemolytica, Pasteurella multocida, Pneumocystis carinii, Proteus mirabilis, Proteus vulgaris, Pseudomonas aeruginosa, Pseudomonas putida, Pseudomonas syringae, Salmonella bongori, Salmonella cholerasuis, Salmonella enterica, Salmonella paratyphi, Salmonella typhi, Salmonella*

15 *typhimurium, Shigella boydii, Shigella dysenteriae, Shigella flexneri, Shigella sonnei, Staphylococcus aureus, Staphylococcus epidermidis, Staphylococcus haemolyticus, Streptococcus pneumoniae, Streptococcus mutans, Streptococcus pyogenes, Treponema pallidum, Ureaplasma urealyticum, Vibrio cholerae, Vibrio parahaemolyticus, Vibrio vulnificans, Yersinia enterocolitica,. Yersinia pestis* and any species falling within the genera of any of the above species.

20   41.   The method of Paragraph 39, wherein said method comprises inhibiting said activity or reducing said amount of a gene product in an organism other than *E. coli.*

42.   The method of Paragraph 39, wherein said gene product is present in an organism other than *E. coli.*

43.   The method of Paragraph 39, wherein said gene product comprises a polypeptide

25 comprising a sequence selected from the group consisting of SEQ ID NOs.: 42398-78581.

44.   A method for identifying a compound which influences the activity of a gene product required for proliferation, said gene product comprising a gene product whose expression is inhibited by an antisense nucleic acid comprising a nucleotide sequence selected from the group consisting of SEQ ID NOs.: 1-6213, said method comprising:

30   contacting said gene product with a candidate compound; and

                determining whether said compound influences the activity of said gene product.

45.   The method of Paragraph 44, wherein said gene product is from an organism selected from the group consisting of *Acinetobacter baumannii, Anaplasma marginale, Aspergillus fumigatus, Bacillus anthracis, Bacteroides fragilis, Bordetella pertussis, Borrelia burgdorferi,*

35 *Burkholderia cepacia, Burkholderia fungorum, Burkholderia mallei, Campylobacter jejuni, Candida albicans, Candida glabrata* (also called *Torulopsis glabrata*), *Candida tropicalis, Candida parapsilosis, Candida guilliermondii, Candida krusei, Candida kefyr* (also called *Candida pseudotropicalis*), *Candida dubliniensis, Chlamydia pneumoniae, Chlamydia trachomatis,*

Clostridium acetobutylicum, Clostridium botulinum, Clostridium difficile, Clostridium perfringens, Coccidioides immitis, Corynebacterium diptheriae, Cryptococcus neoformans, Enterobacter cloacae, Enterococcus faecalis, Enterococcus faecium, Escherichia coli, Haemophilus influenzae, Helicobacter pylori, Histoplasma capsulatum, Klebsiella pneumoniae, Legionella pneumophila, Listeria monocytogenes, Moraxella catarrhalis, Mycobacterium avium, Mycobacterium bovis, Mycobacterium leprae, Mycobacterium tuberculosis, Mycoplasma genitalium, Mycoplasma pneumoniae, Neisseria gonorrhoeae, Neisseria meningitidis, Nocardia asteroides, Pasteurella haemolytica, Pasteurella multocida, Pneumocystis carinii, Proteus mirabilis, Proteus vulgaris, Pseudomonas aeruginosa, Pseudomonas putida, Pseudomonas syringae, Salmonella bongori, Salmonella cholerasuis, Salmonella enterica, Salmonella paratyphi, Salmonella typhi, Salmonella typhimurium, Shigella boydii, Shigella dysenteriae, Shigella flexneri, Shigella sonnei, Staphylococcus aureus, Staphylococcus epidermidis, Staphylococcus haemolyticus, Streptococcus pneumoniae, Streptococcus mutans, Streptococcus pyogenes, Treponema pallidum, Ureaplasma urealyticum, Vibrio cholerae, Vibrio parahaemolyticus, Vibrio vulnificans, Yersinia enterocolitica, Yersinia pestis and any species falling within the genera of any of the above species.

46.   The method of Paragraph 44, wherein said gene product is from an organism other than *E. coli.*

47.   The method of Paragraph 44, wherein said gene product is a polypeptide and said activity is an enzymatic activity.

48.   The method of Paragraph 44, wherein said gene product is a polypeptide and said activity is a carbon compound catabolism activity.

49.   The method of Paragraph 44, wherein said gene product is a polypeptide and said activity is a biosynthetic activity.

50.   The method of Paragraph 44, wherein said gene product is a polypeptide and said activity is a transporter activity.

51.   The method of Paragraph 44, wherein said gene product is a polypeptide and said activity is a transcriptional activity.

52.   The method of Paragraph 44, wherein said gene product is a polypeptide and said activity is a DNA replication activity.

53.   The method of Paragraph 44, wherein said gene product is a polypeptide and said activity is a cell division activity.

54.   The method of Paragraph 44, wherein said gene product is an RNA.

55.   The method of Paragraph 44, wherein said gene product is a polypeptide comprising an amino acid sequence selected from the group consisting of SEQ ID NOs.: 42398-78581.

56.   A compound identified using the method of Paragraph 44.

57.   A method for identifying a compound or nucleic acid having the ability to reduce the activity or level of a gene product required for proliferation, said gene product comprising a

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gene product whose activity or expression is inhibited by an antisense nucleic acid comprising a nucleotide sequence selected from the group consisting of SEQ ID NOs.: 1-6213, said method comprising:

(a) contacting a target gene or RNA encoding said gene product with a candidate

5   compound or nucleic acid; and

(b) measuring an activity of said target.

58.   The method of Paragraph 57, wherein said target gene or RNA is from an organism selected from the group consisting of *Acinetobacter baumannii, Anaplasma marginale, Aspergillus fumigatus, Bacillus anthracis, Bacteroides fragilis, Bordetella pertussis, Borrelia burgdorferi,*

10   *Burkholderia cepacia, Burkholderia fungorum, Burkholderia mallei, Campylobacter jejuni, Candida albicans, Candida glabrata* (also called *Torulopsis glabrata), Candida tropicalis, Candida parapsilosis, Candida guilliermondii, Candida krusei, Candida kefyr* (also called *Candida pseudotropicalis), Candida dubliniensis, Chlamydia pneumoniae, Chlamydia trachomatis, Clostridium acetobutylicum, Clostridium botulinum, Clostridium difficile, Clostridium perfringens,*

15   *Coccidioides immitis, Corynebacterium diptheriae, Cryptococcus neoformans, Enterobacter cloacae, Enterococcus faecalis, Enterococcus faecium, Escherichia coli, Haemophilus influenzae, Helicobacter pylori, Histoplasma capsulatum, Klebsiella pneumoniae, Legionella pneumophila, Listeria monocytogenes, Moraxella catarrhalis, Mycobacterium avium, Mycobacterium bovis, Mycobacterium leprae, Mycobacterium tuberculosis, Mycoplasma genitalium, Mycoplasma*

20   *pneumoniae, Neisseria gonorrhoeae, Neisseria meningitidis, Nocardia asteroides, Pasteurella haemolytica, Pasteurella multocida, Pneumocystis carinii, Proteus mirabilis, Proteus vulgaris, Pseudomonas aeruginosa, Pseudomonas putida, Pseudomonas syringae, Salmonella bongori, Salmonella cholerasuis, Salmonella enterica, Salmonella paratyphi, Salmonella typhi, Salmonella typhimurium, Shigella boydii, Shigella dysenteriae, Shigella flexneri, Shigella sonnei,*

25   *Staphylococcus aureus, Staphylococcus epidermidis, Staphylococcus haemolyticus, Streptococcus pneumoniae, Streptococcus mutans, Streptococcus pyogenes, Treponema pallidum, Ureaplasma urealyticum, Vibrio cholerae, Vibrio parahaemolyticus, Vibrio vulnificans, Yersinia enterocolitica, Yersinia pestis* and any species falling within the genera of any of the above species.

59.   The method of Paragraph 57, wherein said target gene or RNA is from an organism

30   other than *E. coli.*

60.   The method of Paragraph 57, wherein said gene product is from an organism other than *E. coli.*

61.   The method of Paragraph 57, wherein said target is a messenger RNA molecule and said activity is translation of said messenger RNA.

35   62.   The method of Paragraph 57, wherein said target is a messenger RNA molecule and said activity is transcription of a gene encoding said messenger RNA.

63.   The method of Paragraph 57, wherein said target is a gene and said activity is transcription of said gene.

64.   The method of Paragraph 57, wherein said target is a nontranslated RNA and said activity is processing or folding of said nontranslated RNA or assembly of said nontranslated RNA into a protein/RNA complex.

65.   The method of Paragraph 57, wherein said target is a messenger RNA molecule encoding a polypeptide comprising an amino acid sequence selected from the group consisting of SEQ ID NOs.: 42398-78581.

66.   The method of Paragraph 57, wherein said target comprises a nucleic acid selected from the group consisting of SEQ ID NOS.: 6214-42397.

67.   A compound or nucleic acid identified using the method of Paragraph 57.

68.   A method for identifying a compound which reduces the activity or level of a gene product required for proliferation of a cell, wherein the activity or expression of said gene product is inhibited by an antisense nucleic acid comprising a nucleotide sequence selected from the group consisting of SEQ ID NOs.: 1-6213, said method comprising the steps of:

(a) providing a sublethal level of an antisense nucleic acid comprising a nucleotide sequence complementary to a nucleic acid comprising a nucleotide sequence encoding said gene product in a cell to reduce the activity or amount of said gene product in said cell, thereby producing a sensitized cell;

(b) contacting said sensitized cell with a compound; and

(c) determining the degree to which said compound inhibits proliferation of said sensitized cell relative to a cell which does not contain said antisense nucleic acid.

69.   The method of Paragraph 68, wherein said determining step comprises determining whether said compound inhibits the growth of said sensitized cell to a greater extent than said compound inhibits the growth of a nonsensitized cell.

70.   The method of Paragraph 68, wherein said cell is a Gram positive bacterium.

71.   The method of Paragraph 68, wherein said Gram positive bacterium is selected from the group consisting of *Staphylococcus* species, *Streptococcus* species, *Enterococcus* species, *Mycobacterium* species, *Clostridium* species, and *Bacillus* species.

72.   The method of Paragraph 68, wherein said bacterium is *Staphylococcus aureus*.

73.   The method of Paragraph 72, wherein said *Staphylococcus* species is coagulase negative.

74.   The method of Paragraph 72, wherein said bacterium is selected from the group consisting of *Staphylococcus aureus* RN450 and *Staphylococcus aureus* RN4220.

75.   The method of Paragraph 68, wherein said cell is an organism selected from the group consisting of *Acinetobacter baumannii, Anaplasma marginale, Aspergillus fumigatus, Bacillus anthracis, Bacteroides fragilis, Bordetella pertussis, Borrelia burgdorferi, Burkholderia cepacia, Burkholderia fungorum, Burkholderia mallei, Campylobacter jejuni, Candida albicans, Candida glabrata* (also called *Torulopsis glabrata*), *Candida tropicalis, Candida parapsilosis, Candida guilliermondii, Candida krusei, Candida kefyr* (also called *Candida pseudotropicalis*),

Candida dubliniensis, Chlamydia pneumoniae, Chlamydia trachomatis, Clostridium acetobutylicum, Clostridium botulinum, Clostridium difficile, Clostridium perfringens, Coccidioides immitis, Corynebacterium diptheriae, Cryptococcus neoformans, Enterobacter cloacae, Enterococcus faecalis, Enterococcus faecium, Escherichia coli, Haemophilus influenzae, Helicobacter pylori, Histoplasma capsulatum, Klebsiella pneumoniae, Legionella pneumophila, Listeria monocytogenes, Moraxella catarrhalis, Mycobacterium avium, Mycobacterium bovis, Mycobacterium leprae, Mycobacterium tuberculosis, Mycoplasma genitalium, Mycoplasma pneumoniae, Neisseria gonorrhoeae, Neisseria meningitidis, Nocardia asteroides, Pasteurella haemolytica, Pasteurella multocida, Pneumocystis carinii, Proteus mirabilis, Proteus vulgaris, Pseudomonas aeruginosa, Pseudomonas putida, Pseudomonas syringae, Salmonella bongori, Salmonella cholerasuis, Salmonella enterica, Salmonella paratyphi, Salmonella typhi, Salmonella typhimurium, Shigella boydii, Shigella dysenteriae, Shigella flexneri, Shigella sonnei, Staphylococcus aureus, Staphylococcus epidermidis, Staphylococcus haemolyticus, Streptococcus pneumoniae, Streptococcus mutans, Streptococcus pyogenes, Treponema pallidum, Ureaplasma urealyticum, Vibrio cholerae, Vibrio parahaemolyticus, Vibrio vulnificans, Yersinia enterocolitica, Yersinia pestis and any species falling within the genera of any of the above species.

76.   The method of Paragraph 68, wherein said cell is not an *E. coli* cell.

77.   The method of Paragraph 68, wherein said gene product is from an organism other than *E. coli*.

78.   The method of Paragraph 68, wherein said antisense nucleic acid is transcribed from an inducible promoter.

79.   The method of Paragraph 68, further comprising the step of contacting said cell with a concentration of inducer which induces transcription of said antisense nucleic acid to a sublethal level.

80.   The method of Paragraph 68, wherein growth inhibition is measured by monitoring optical density of a culture growth solution.

81.   The method of Paragraph 68, wherein said gene product is a polypeptide.

82.   The method of Paragraph 81, wherein said polypeptide comprises an amino acid sequence selected from the group consisting of SEQ ID NOs.: 42398-78581.

83.   The method of Paragraph 68, wherein said gene product is an RNA.

84.   The method of Paragraph 68, wherein nucleic acid encoding said gene product comprises a nucleotide sequence selected from the group consisting of SEQ ID NOS.: 6214-42397.

85.   A compound identified using the method of Paragraph 68.

86.   A method for inhibiting cellular proliferation comprising introducing an effective amount of a compound with activity against a gene whose activity or expression is inhibited by an antisense nucleic acid comprising a nucleotide sequence selected from the group consisting of SEQ ID NOs.: 1-6213 or a compound with activity against the product of said gene into a population of cells expressing said gene.

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87.   The method of Paragraph 86, wherein said compound is an antisense nucleic acid comprising a nucleotide sequence selected from the group consisting of SEQ ID NOs.: 1-6213, or a proliferation-inhibiting portion thereof.

88.   The method of Paragraph 86, wherein said proliferation inhibiting portion of one of SEQ ID NOs.: 1-6213 is a fragment comprising at least 10, at least 20, at least 25, at least 30, at least 50 or more than 51 consecutive nucleotides of one of SEQ ID NOs.: 1-6213.

89.   The method of Paragraph 86, wherein said population is a population of Gram positive bacteria.

90.   The method of Paragraph 89, wherein said population of Gram positive bacteria is selected from the group consisting of a population of *Staphylococcus* species, *Streptococcus* species, *Enterococcus* species, *Mycobacterium* species, *Clostridium* species, and *Bacillus* species.

91.   The method of Paragraph 86, wherein said population is a population of *Staphylococcus aureus*.

92.   The method of Paragraph 91, wherein said population is a population of a bacterium selected from the group consisting of *Staphylococcus aureus* RN450 and *Staphylococcus aureus* RN4220.

93.   The method of Paragraph 86, wherein said population is a population of a bacterium selected from the group consisting of *Acinetobacter baumannii, Anaplasma marginale, Aspergillus fumigatus, Bacillus anthracis, Bacteroides fragilis, Bordetella pertussis, Borrelia burgdorferi, Burkholderia cepacia, Burkholderia fungorum, Burkholderia mallei, Campylobacter jejuni, Candida albicans, Candida glabrata* (also called *Torulopsis glabrata*), *Candida tropicalis, Candida parapsilosis, Candida guilliermondii, Candida krusei, Candida kefyr* (also called *Candida pseudotropicalis*), *Candida dubliniensis, Chlamydia pneumoniae, Chlamydia trachomatis, Clostridium acetobutylicum, Clostridium botulinum, Clostridium difficile, Clostridium perfringens, Coccidioides immitis, Corynebacterium diptheriae, Cryptococcus neoformans, Enterobacter cloacae, Enterococcus faecalis, Enterococcus faecium, Escherichia coli, Haemophilus influenzae, Helicobacter pylori, Histoplasma capsulatum, Klebsiella pneumoniae, Legionella pneumophila, Listeria monocytogenes, Moraxella catarrhalis, Mycobacterium avium, Mycobacterium bovis, Mycobacterium leprae, Mycobacterium tuberculosis, Mycoplasma genitalium, Mycoplasma pneumoniae, Neisseria gonorrhoeae, Neisseria meningitidis, Nocardia asteroides, Pasteurella haemolytica, Pasteurella multocida, Pneumocystis carinii, Proteus mirabilis, Proteus vulgaris, Pseudomonas aeruginosa, Pseudomonas putida, Pseudomonas syringae, Salmonella bongori, Salmonella cholerasuis, Salmonella enterica, Salmonella paratyphi, Salmonella typhi, Salmonella typhimurium, Shigella boydii, Shigella dysenteriae, Shigella flexneri, Shigella sonnei, Staphylococcus aureus, Staphylococcus epidermidis, Staphylococcus haemolyticus, Streptococcus pneumoniae, Streptococcus mutans, Streptococcus pyogenes, Treponema pallidum, Ureaplasma urealyticum, Vibrio cholerae, Vibrio parahaemolyticus, Vibrio vulnificans, Yersinia enterocolitica, Yersinia pestis* and any species falling within the genera of any of the above species.

94.   The method of Paragraph 86, wherein said population is a population of an organism other than *E. coli*.

95.   The method of Paragraph 86, wherein said product of said gene is from an organism other than *E. coli*.

96.   The method of Paragraph 86, wherein said gene encodes a polypeptide comprising an amino acid sequence selected from the group consisting of SEQ ID NOs.: 42398-78581.

97.   The method of Paragraph 86, wherein said gene comprises a nucleotide sequence selected from the group consisting of SEQ ID NOS.: 6214-42397.

98.   A composition comprising an effective concentration of an antisense nucleic acid comprising a nucleotide sequence selected from the group consisting of SEQ ID NOs.: 1-6213, or a proliferation-inhibiting portion thereof in a pharmaceutically acceptable carrier.

99.   The composition of Paragraph 98, wherein said proliferation-inhibiting portion of one of SEQ ID NOs.: 1-6213 comprises at least 20, at least 25, at least 30, at least 50 or more than 50 consecutive nucleotides of one of SEQ ID NOs.: 1-6213.

100.   A method for inhibiting the activity or expression of a gene in an operon required for proliferation wherein the activity or expression of at least one gene in said operon is inhibited by an antisense nucleic acid comprising a sequence selected from the group consisting of SEQ ID NOs.: 1-6213, said method comprising contacting a cell in a cell population with an antisense nucleic acid complementary to at least a portion of said operon.

101.   The method of Paragraph 100, wherein said antisense nucleic acid comprises a nucleotide sequence selected from the group consisting of SEQ ID NOs.: 1-6213 or a proliferation-inhibiting portion thereof.

102.   The method of Paragraph 100, wherein said cell is selected from the group consisting of *Acinetobacter baumannii, Anaplasma marginale, Aspergillus fumigatus, Bacillus anthracis, Bacteroides fragilis, Bordetella pertussis, Borrelia burgdorferi, Burkholderia cepacia, Burkholderia fungorum, Burkholderia mallei, Campylobacter jejuni, Candida albicans, Candida glabrata* (also called *Torulopsis glabrata*), *Candida tropicalis, Candida parapsilosis, Candida guilliermondii, Candida krusei, Candida kefyr* (also called *Candida pseudotropicalis*), *Candida dubliniensis, Chlamydia pneumoniae, Chlamydia trachomatis, Clostridium acetobutylicum, Clostridium botulinum, Clostridium difficile, Clostridium perfringens, Coccidioides immitis, Corynebacterium diptheriae, Cryptococcus neoformans, Enterobacter cloacae, Enterococcus faecalis, Enterococcus faecium, Escherichia coli, Haemophilus influenzae, Helicobacter pylori, Histoplasma capsulatum, Klebsiella pneumoniae, Legionella pneumophila, Listeria monocytogenes, Moraxella catarrhalis, Mycobacterium avium, Mycobacterium bovis, Mycobacterium leprae, Mycobacterium tuberculosis, Mycoplasma genitalium, Mycoplasma pneumoniae, Neisseria gonorrhoeae, Neisseria meningitidis, Nocardia asteroides, Pasteurella haemolytica, Pasteurella multocida, Pneumocystis carinii, Proteus mirabilis, Proteus vulgaris, Pseudomonas aeruginosa, Pseudomonas putida, Pseudomonas syringae, Salmonella bongori,*

Salmonella cholerasuis, Salmonella enterica, Salmonella paratyphi, Salmonella typhi, Salmonella typhimurium, Shigella boydii, Shigella dysenteriae, Shigella flexneri, Shigella sonnei, Staphylococcus aureus, Staphylococcus epidermidis, Staphylococcus haemolyticus, Streptococcus pneumoniae, Streptococcus mutans, Streptococcus pyogenes, Treponema pallidum, Ureaplasma urealyticum, Vibrio cholerae, Vibrio parahaemolyticus, Vibrio vulnificans, Yersinia enterocolitica, Yersinia pestis and any species falling within the genera of any of the above species.

103. The method of Paragraph 100, wherein said cell is not an *E. coli* cell.

104. The method of Paragraph 100, wherein said gene is from an organism other than *E. coli.*

105. The method of Paragraph 100, wherein said cell is contacted with said antisense nucleic acid by introducing a plasmid which expresses said antisense nucleic acid into said cell population.

106. The method of Paragraph 100, wherein said cell is contacted with said antisense nucleic acid by introducing a phage which encodes said antisense nucleic acid into said cell population.

107. The method of Paragraph 100, wherein said cell is contacted with said antisense nucleic acid by expressing said antisense nucleic acid from the chromosome of cells in said cell population.

108. The method of Paragraph 100, wherein said cell is contacted with said antisense nucleic acid by introducing a promoter adjacent to a chromosomal copy of said antisense nucleic acid such that said promoter directs the transcription of said antisense nucleic acid.

109. The method of Paragraph 100, wherein said cell is contacted with said antisense nucleic acid by introducing a retron which expresses said antisense nucleic acid into said cell population.

110. The method of Paragraph 100, wherein said cell is contacted with said antisense nucleic acid by introducing a ribozyme into said cell-population, wherein a binding portion of said ribozyme comprises said antisense nucleic acid.

111. The method of Paragraph 100, wherein said cell is contacted with said antisense nucleic acid by introducing a liposome comprising said antisense nucleic acid into said cell.

112. The method of Paragraph 100, wherein said cell is contacted with said antisense nucleic acid by electroporation of said antisense nucleic acid into said cell.

113. The method of Paragraph 100, wherein said antisense nucleic acid is a fragment comprising at least 10, at least 20, at least 25, at least 30, at least 50 or more than 50 consecutive nucleotides of one of SEQ ID NOs.: 1-6213.

114. The method of Paragraph 100 wherein said antisense nucleic acid is a synthetic oligonucleotide.

115. The method of Paragraph 100, wherein said gene comprises a nucleotide sequence selected from the group consisting of SEQ ID NOS.: 6214-42397.

116.   A method for identifying a gene which is required for proliferation of a cell comprising:

(a) contacting a cell with an antisense nucleic acid comprising a nucleotide sequence selected from the group consisting of SEQ ID NOs.: 1-6213, wherein said cell is a cell other than the organism from which said nucleic acid was obtained;

(b) determining whether said nucleic acid inhibits proliferation of said cell; and

(c) identifying the gene in said cell which encodes the mRNA which is complementary to said antisense nucleic acid or a portion thereof.

117.   The method of Paragraph 116, wherein said cell is selected from the group consisting of *Staphylococcus* species, *Streptococcus* species, *Enterococcus* species, *Mycobacterium* species, *Clostridium* species, and *Bacillus* species.

118.   The method of Paragraph 116 wherein said cell is selected from the group consisting of *Acinetobacter baumannii, Anaplasma marginale, Aspergillus fumigatus, Bacillus anthracis, Bacteroides fragilis, Bordetella pertussis, Borrelia burgdorferi, Burkholderia cepacia, Burkholderia fungorum, Burkholderia mallei, Campylobacter jejuni, Candida albicans, Candida glabrata* (also called *Torulopsis glabrata*), *Candida tropicalis, Candida parapsilosis, Candida guilliermondii, Candida krusei, Candida kefyr* (also called *Candida pseudotropicalis*), *Candida dubliniensis, Chlamydia pneumoniae, Chlamydia trachomatis, Clostridium acetobutylicum, Clostridium botulinum, Clostridium difficile, Clostridium perfringens, Coccidioides immitis, Corynebacterium diptheriae, Cryptococcus neoformans, Enterobacter cloacae, Enterococcus faecalis, Enterococcus faecium, Escherichia coli, Haemophilus influenzae, Helicobacter pylori, Histoplasma capsulatum, Klebsiella pneumoniae, Legionella pneumophila, Listeria monocytogenes, Moraxella catarrhalis, Mycobacterium avium, Mycobacterium bovis, Mycobacterium leprae, Mycobacterium tuberculosis, Mycoplasma genitalium, Mycoplasma pneumoniae, Neisseria gonorrhoeae, Neisseria meningitidis, Nocardia asteroides, Pasteurella haemolytica, Pasteurella multocida, Pneumocystis carinii, Proteus mirabilis, Proteus vulgaris, Pseudomonas aeruginosa, Pseudomonas putida, Pseudomonas syringae, Salmonella bongori, Salmonella cholerasuis, Salmonella enterica, Salmonella paratyphi, Salmonella typhi, Salmonella typhimurium, Shigella boydii, Shigella dysenteriae, Shigella flexneri, Shigella sonnei, Staphylococcus aureus, Staphylococcus epidermidis, Staphylococcus haemolyticus, Streptococcus pneumoniae, Streptococcus mutans, Streptococcus pyogenes, Treponema pallidum, Ureaplasma urealyticum, Vibrio cholerae, Vibrio parahaemolyticus, Vibrio vulnificans, Yersinia enterocolitica, Yersinia pestis* and any species falling within the genera of any of the above species.

119.   The method of Paragraph 116, wherein said cell is not *E. coli*.

120.   The method of Paragraph 116, further comprising operably linking said antisense nucleic acid to a promoter which is functional in said cell, said promoter being included in a vector, and introducing said vector into said cell.

121.   A method for identifying a compound having the ability to inhibit proliferation of a cell comprising:

(a) identifying a homolog of a gene or gene product whose activity or level is inhibited by a nucleic acid comprising a nucleotide sequence selected from the group consisting of SEQ ID NOs. 1-6213 in a test cell, wherein said test cell is not the cell from which said nucleic acid was obtained;

(b) identifying an inhibitory nucleic acid sequence which inhibits the activity of said homolog in said test cell;

(c) contacting said test cell with a sublethal level of said inhibitory nucleic acid, thus sensitizing said cell;

(d) contacting the sensitized cell of step (c) with a compound; and

(e) determining the degree to which said compound inhibits proliferation of said sensitized cell relative to a cell which does not contain said inhibitory nucleic acid.

122.   The method of Paragraph 121, wherein said determining step comprises determining whether said compound inhibits proliferation of said sensitized test cell to a greater extent than said compound inhibits proliferation of a nonsensitized test cell.

123.   The method of Paragraph 121, wherein step (a) comprises identifying a nucleic acid homologous to a gene or gene product whose activity or level is inhibited by a nucleic acid selected from the group consisting of SEQ ID NOs. 1-6213 or a nucleic acid encoding a homologous polypeptide to a polypeptide whose activity or level is inhibited by a nucleic acid selected from the group consisting of SEQ ID NOs. 1-6213 by using an algorithm selected from the group consisting of BLASTN version 2.0 with the default parameters and FASTA version 3.0t78 algorithm with the default parameters to identify said homologous nucleic acid or said nucleic acid encoding a homologous polypeptide in a database.

124.   The method of Paragraph 121 wherein said step (a) comprises identifying a homologous nucleic acid or a nucleic acid comprising a sequence of nucleotides encoding a homologous polypeptide by identifying nucleic acids which hybridize to said nucleic acid selected from the group consisting of SEQ ID NOs. 1-6213 or the complement of said nucleic acid selected from the group consisting of SEQ ID NOs. 1-6213.

125.   The method of Paragraph 121 wherein step (a) comprises expressing a nucleic acid selected from the group consisting of SEQ ID NOs. 1-6213 in said test cell.

126.   The method of Paragraph 121, wherein step (a) comprises identifying a homologous nucleic acid or a nucleic acid encoding a homologous polypeptide in a test cell selected from the group consisting of *Acinetobacter baumannii, Anaplasma marginale, Aspergillus fumigatus, Bacillus anthracis, Bacteroides fragilis, Bordetella pertussis, Borrelia burgdorferi, Burkholderia cepacia, Burkholderia fungorum, Burkholderia mallei, Campylobacter jejuni, Candida albicans, Candida glabrata* (also called *Torulopsis glabrata*), *Candida tropicalis, Candida parapsilosis, Candida guilliermondii, Candida krusei, Candida kefyr* (also called *Candida*

pseudotropicalis), *Candida dubliniensis*, *Chlamydia · pneumoniae*, *Chlamydia trachomatis*, *Clostridium acetobutylicum*, *Clostridium botulinum*, *Clostridium difficile*, *Clostridium perfringens*, *Coccidioides immitis*, *Corynebacterium diptheriae*, *Cryptococcus neoformans*, *Enterobacter cloacae*, *Enterococcus faecalis*, *Enterococcus faecium*, *Escherichia coli*, *Haemophilus influenzae*,

5   *Helicobacter pylori*, *Histoplasma capsulatum*, *Klebsiella pneumoniae*, *Legionella pneumophila*, *Listeria monocytogenes*, *Moraxella catarrhalis*, *Mycobacterium avium*, *Mycobacterium bovis*, *Mycobacterium leprae*, *Mycobacterium tuberculosis*, *Mycoplasma genitalium*, *Mycoplasma pneumoniae*, *Neisseria gonorrhoeae*, *Neisseria meningitidis*, *Nocardia asteroides*, *Pasteurella haemolytica*, *Pasteurella multocida*, *Pneumocystis carinii*, *Proteus mirabilis*, *Proteus vulgaris*,

10 *Pseudomonas aeruginosa*, *Pseudomonas putida*, *Pseudomonas syringae*, *Salmonella bongori*, *Salmonella cholerasuis*, *Salmonella enterica*, *Salmonella paratyphi*, *Salmonella typhi*, *Salmonella typhimurium*, *Shigella boydii*, *Shigella dysenteriae*, *Shigella flexneri*, *Shigella sonnei*, *Staphylococcus aureus*, *Staphylococcus epidermidis*, *Staphylococcus haemolyticus*, *Streptococcus pneumoniae*, *Streptococcus mutans*, *Streptococcus pyogenes*, *Treponema pallidum*, *Ureaplasma*

15 *urealyticum*, *Vibrio cholerae*, *Vibrio parahaemolyticus*, *Vibrio vulnificans*, *Yersinia enterocolitica*, *Yersinia pestis* and any species falling within the genera of any of the above species.

127.   The method of Paragraph 121, wherein step (a) comprises identifying a homologous nucleic acid or a nucleic acid encoding a homologous polypeptide in a test cell other than *E. coli*.

20   128.   The method of Paragraph 121, wherein said inhibitory nucleic acid is an antisense nucleic acid.

129.   The method of Paragraph 121, wherein said inhibitory nucleic acid comprises an antisense nucleic acid to a portion of said homolog.

130.   The method of Paragraph 121, wherein said inhibitory nucleic acid comprises an

25 antisense nucleic acid to a portion of the operon encoding said homolog.

131.   The method of Paragraph 121, wherein the step of contacting the cell with a sublethal level of said inhibitory nucleic acid comprises directly contacting the surface of said cell with said inhibitory nucleic acid.

132.   The method of Paragraph 121, wherein the step of contacting the cell with a

30 sublethal level of said inhibitory nucleic acid comprises transcribing an antisense nucleic acid complementary to at least a portion of the RNA transcribed from said homolog in said cell.

133.   The method of Paragraph 121, wherein said gene product comprises a polypeptide comprising an amino acid sequence selected from the group consisting of SEQ ID NOs.: 42398-78581.

35   134.   The method of Paragraph 121, wherein said gene comprises a nucleotide sequence selected from the group consisting of SEQ ID NOS.: 6214-42397.

135.   A compound identified using the method of Paragraph 121.

136. A method of identifying a compound having the ability to inhibit proliferation comprising:

    (a) contacting a test cell with a sublethal level of a nucleic acid comprising a nucleotide sequence selected from the group consisting of SEQ ID NOs. 1-6213 or a portion thereof which inhibits the proliferation of the cell from which said nucleic acid was obtained, thus sensitizing said test cell;

    (b) contacting the sensitized test cell of step (a) with a compound; and

    (c) determining the degree to which said compound inhibits proliferation of said sensitized test cell relative to a cell which does not contain said nucleic acid.

137. The method of Paragraph 136, wherein said determining step comprises determining whether said compound inhibits proliferation of said sensitized test cell to a greater extent than said compound inhibits proliferation of a nonsensitized test cell.

138. A compound identified using the method of Paragraph 136.

139. The method of Paragraph 136, wherein said test cell is selected from the group consisting of *Acinetobacter baumannii, Anaplasma marginale, Aspergillus fumigatus, Bacillus anthracis, Bacteroides fragilis, Bordetella pertussis, Borrelia burgdorferi, Burkholderia cepacia, Burkholderia fungorum, Burkholderia mallei, Campylobacter jejuni, Candida albicans, Candida glabrata* (also called *Torulopsis glabrata*), *Candida tropicalis, Candida parapsilosis, Candida guilliermondii, Candida krusei, Candida kefyr* (also called *Candida pseudotropicalis*), *Candida dubliniensis, Chlamydia pneumoniae, Chlamydia trachomatis, Clostridium acetobutylicum, Clostridium botulinum, Clostridium difficile, Clostridium perfringens, Coccidioides immitis, Corynebacterium diptheriae, Cryptococcus neoformans, Enterobacter cloacae, Enterococcus faecalis, Enterococcus faecium, Escherichia coli, Haemophilus influenzae, Helicobacter pylori, Histoplasma capsulatum, Klebsiella pneumoniae, Legionella pneumophila, Listeria monocytogenes, Moraxella catarrhalis, Mycobacterium avium, Mycobacterium bovis, Mycobacterium leprae, Mycobacterium tuberculosis, Mycoplasma genitalium, Mycoplasma pneumoniae, Neisseria gonorrhoeae, Neisseria meningitidis, Nocardia asteroides, Pasteurella haemolytica, Pasteurella multocida, Pneumocystis carinii, Proteus mirabilis, Proteus vulgaris, Pseudomonas aeruginosa, Pseudomonas putida, Pseudomonas syringae, Salmonella bongori, Salmonella cholerasuis, Salmonella enterica, Salmonella paratyphi, Salmonella typhi, Salmonella typhimurium, Shigella boydii, Shigella dysenteriae, Shigella flexneri, Shigella sonnei, Staphylococcus aureus, Staphylococcus epidermidis, Staphylococcus haemolyticus, Streptococcus pneumoniae, Streptococcus mutans, Streptococcus pyogenes, Treponema pallidum, Ureaplasma urealyticum, Vibrio cholerae, Vibrio parahaemolyticus, Vibrio vulnificans, Yersinia enterocolitica, Yersinia pestis* and any species falling within the genera of any of the above species.

140. The method of Paragraph 136, wherein the test cell is not *E. coli.*

141. A method for identifying a compound having activity against a biological pathway required for proliferation comprising:

(a) sensitizing a cell by providing a sublethal level of an antisense nucleic acid complementary to a nucleic acid encoding a gene product required for proliferation, wherein the activity or expression of said gene product is inhibited by an antisense nucleic acid comprising a nucleotide sequence selected from the group consisting of SEQ ID

5   NOs.: 1-6213, in said cell to reduce the activity or amount of said gene product;

(b) contacting the sensitized cell with a compound; and

(c) determining the degree to which said compound inhibits the growth of said sensitized cell relative to a cell which does not contain said antisense nucleic acid.

142.   The method of Paragraph 141, wherein said determining step comprises

10   determining whether said compound inhibits the growth of said sensitized cell to a greater extent than said compound inhibits the growth of a nonsensitized cell.

143.   The method of Paragraph 141, wherein said cell is selected from the group consisting of bacterial cells, fungal cells, plant cells, and animal cells.

144.   The method of Paragraph 141, wherein said cell is a Gram positive bacterium.

15   145.   The method of Paragraph 144, wherein said Gram positive bacterium is selected from the group consisting of *Staphylococcus* species, *Streptococcus* species, *Enterococcus* species, *Mycobacterium* species, *Clostridium* species, and *Bacillus* species.

146.   The method of Paragraph 145, wherein said Gram positive bacterium is *Staphylococcus aureus*.

20   147.   The method of Paragraph 146, wherein said Gram positive bacterium is selected from the group consisting of *Staphylococcus aureus* RN450 and *Staphylococcus aureus* RN4220.

148.   The method of Paragraph 141, wherein said cell is selected from the group consisting of *Acinetobacter baumannii, Anaplasma marginale, Aspergillus fumigatus, Bacillus anthracis, Bacteroides fragilis, Bordetella pertussis, Borrelia burgdorferi, Burkholderia cepacia,*

25   *Burkholderia fungorum, Burkholderia mallei, Campylobacter jejuni, Candida albicans, Candida glabrata* (also called *Torulopsis glabrata*), *Candida tropicalis, Candida parapsilosis, Candida guilliermondii, Candida krusei, Candida kefyr* (also called *Candida pseudotropicalis*), *Candida dubliniensis, Chlamydia pneumoniae, Chlamydia trachomatis, Clostridium acetobutylicum, Clostridium botulinum, Clostridium difficile, Clostridium perfringens, Coccidioides immitis,*

30   *Corynebacterium diptheriae, Cryptococcus neoformans, Enterobacter cloacae, Enterococcus faecalis, Enterococcus faecium, Escherichia coli, Haemophilus influenzae, Helicobacter pylori, Histoplasma capsulatum, Klebsiella pneumoniae, Legionella pneumophila, Listeria monocytogenes, Moraxella catarrhalis, Mycobacterium avium, Mycobacterium bovis, Mycobacterium leprae, Mycobacterium tuberculosis, Mycoplasma genitalium, Mycoplasma*

35   *pneumoniae, Neisseria gonorrhoeae, Neisseria meningitidis, Nocardia asteroides, Pasteurella haemolytica, Pasteurella multocida, Pneumocystis carinii, Proteus mirabilis, Proteus vulgaris, Pseudomonas aeruginosa, Pseudomonas putida, Pseudomonas syringae, Salmonella bongori, Salmonella cholerasuis, Salmonella enterica, Salmonella paratyphi, Salmonella typhi, Salmonella*

typhimurium, Shigella boydii, Shigella dysenteriae, Shigella flexneri, Shigella sonnei, Staphylococcus aureus, Staphylococcus epidermidis, Staphylococcus haemolyticus, Streptococcus pneumoniae, Streptococcus mutans, Streptococcus pyogenes, Treponema pallidum, Ureaplasma urealyticum, Vibrio cholerae, Vibrio parahaemolyticus, Vibrio vulnificans, Yersinia enterocolitica, Yersinia pestis and any species falling within the genera of any of the above species.

149.   The method of Paragraph 141, wherein said cell is not an *E. coli* cell.

150.   The method of Paragraph 141, wherein said gene product is from an organism other than *E. coli*.

151.   The method of Paragraph 141, wherein said antisense nucleic acid is transcribed from an inducible promoter.

152.   The method of Paragraph 141, further comprising contacting the cell with an agent which induces transcription of said antisense nucleic acid from said inducible promoter, wherein said antisense nucleic acid is transcribed at a sublethal level.

153.   The method of Paragraph 141, wherein inhibition of proliferation is measured by monitoring the optical density of a liquid culture.

154.   The method of Paragraph 141, wherein said gene product comprises a polypeptide comprising an amino acid sequence selected from the group consisting of SEQ ID NOs.: 42398-78581.

155.   The method of Paragraph 141, wherein said nucleic acid encoding said gene product comprises a nucleotide sequence selected from the group consisting of SEQ ID NOS.: 6214-42397.

156.   A compound identified using the method of Paragraph 141.

157.   A method for identifying a compound having the ability to inhibit cellular proliferation comprising:

>   (a) contacting a cell with an agent which reduces the activity or level of a gene product required for proliferation of said cell, wherein said gene product is a gene product whose activity or expression is inhibited by an antisense nucleic acid comprising a nucleotide sequence selected from the group consisting of SEQ ID NOs.: 1-6213;

>   (b) contacting said cell with a compound; and

>   (c) determining whether said compound reduces proliferation of said contacted cell by acting on said gene product.

158.   The method of Paragraph 157, wherein said determining step comprises determining whether said compound reduces proliferation of said contacted cell to a greater extent than said compound reduces proliferation of cells which have not been contacted with said agent.

159.   The method of Paragraph 157, wherein said cell is selected from the group consisting of *Acinetobacter baumannii, Anaplasma marginale, Aspergillus fumigatus, Bacillus anthracis, Bacteroides fragilis, Bordetella pertussis, Borrelia burgdorferi, Burkholderia cepacia, Burkholderia fungorum, Burkholderia mallei, Campylobacter jejuni, Candida albicans, Candida*

glabrata (also called *Torulopsis glabrata*), *Candida tropicalis, Candida parapsilosis, Candida guilliermondii, Candida krusei, Candida kefyr* (also called *Candida pseudotropicalis*), *Candida dubliniensis, Chlamydia pneumoniae, Chlamydia trachomatis, Clostridium acetobutylicum, Clostridium botulinum, Clostridium difficile, Clostridium perfringens, Coccidioides immitis,*

5   *Corynebacterium diptheriae, Cryptococcus neoformans, Enterobacter cloacae, Enterococcus faecalis, Enterococcus faecium, Escherichia coli, Haemophilus influenzae, Helicobacter pylori, Histoplasma capsulatum, Klebsiella pneumoniae, Legionella pneumophila, Listeria monocytogenes, Moraxella catarrhalis, Mycobacterium avium, Mycobacterium bovis, Mycobacterium leprae, Mycobacterium tuberculosis, Mycoplasma genitalium, Mycoplasma*

10   *pneumoniae, Neisseria gonorrhoeae, Neisseria meningitidis, Nocardia asteroides, Pasteurella haemolytica, Pasteurella multocida, Pneumocystis carinii, Proteus mirabilis, Proteus vulgaris, Pseudomonas aeruginosa, Pseudomonas putida, Pseudomonas syringae, Salmonella bongori, Salmonella cholerasuis, Salmonella enterica, Salmonella paratyphi, Salmonella typhi, Salmonella typhimurium, Shigella boydii, Shigella dysenteriae, Shigella flexneri, Shigella sonnei,*

15   *Staphylococcus aureus, Staphylococcus epidermidis, Staphylococcus haemolyticus, Streptococcus pneumoniae, Streptococcus mutans, Streptococcus pyogenes, Treponema pallidum, Ureaplasma urealyticum, Vibrio cholerae, Vibrio parahaemolyticus, Vibrio vulnificans, Yersinia enterocolitica, Yersinia pestis* and any species falling within the genera of any of the above species.

160.   The method of Paragraph 157, wherein said cell is not an *E. coli* cell.

20   161.   The method of Paragraph 157, wherein said gene product is from an organism other than *E. coli*.

162.   The method of Paragraph 157, wherein said agent which reduces the activity or level of a gene product required for proliferation of said cell comprises an antisense nucleic acid to a gene or operon required for proliferation.

25   163.   The method of Paragraph 157, wherein said agent which reduces the activity or level of a gene product required for proliferation of said cell comprises a compound known to inhibit growth or proliferation of a cell.

164.   The method of Paragraph 157, wherein said cell contains a mutation which reduces the activity or level of said gene product required for proliferation of said cell.

30   165.   The method of Paragraph 157, wherein said mutation is a temperature sensitive mutation.

166.   The method of Paragraph 157, wherein said gene product comprises a polypeptide comprising an amino acid sequence selected from the group consisting of SEQ ID NOs.: 42398-78581.

35   167.   A compound identified using the method of Paragraph 157.

168.   A method for identifying the biological pathway in which a proliferation-required gene or its gene product lies, wherein said gene or gene product comprises a gene or gene product

whose activity or expression is inhibited by an antisense nucleic acid comprising a sequence selected from the group consisting of SEQ ID NOs.: 1-6213, said method comprising:

(a) providing a sublethal level of an antisense nucleic acid which inhibits the activity of said proliferation-required gene or gene product in a test cell;

(b) contacting said test cell with a compound known to inhibit growth or proliferation of a cell, wherein the biological pathway on which said compound acts is known; and

(c) determining the degree to which said proliferation of said test cell is inhibited relative to a cell which was not contacted with said compound.

169.   The method of Paragraph 168, wherein said determining step comprises determining whether said test cell has a substantially greater sensitivity to said compound than a cell which does not express said sublethal level of said antisense nucleic acid.

170.   The method of Paragraph 168, wherein said gene product comprises a polypeptide comprising an amino acid sequence selected from the group consisting of SEQ ID NOs.: 42398-78581.

171.   The method of Paragraph 168, wherein said test cell is selected from the group consisting of *Acinetobacter baumannii, Anaplasma marginale, Aspergillus fumigatus, Bacillus anthracis, Bacteroides fragilis, Bordetella pertussis, Borrelia burgdorferi, Burkholderia cepacia, Burkholderia fungorum, Burkholderia mallei, Campylobacter jejuni, Candida albicans, Candida glabrata* (also called *Torulopsis glabrata*), *Candida tropicalis, Candida parapsilosis, Candida guilliermondii, Candida krusei, Candida kefyr* (also called *Candida pseudotropicalis*), *Candida dubliniensis, Chlamydia pneumoniae, Chlamydia trachomatis, Clostridium acetobutylicum, Clostridium botulinum, Clostridium difficile, Clostridium perfringens, Coccidioides immitis, Corynebacterium diptheriae, Cryptococcus neoformans, Enterobacter cloacae, Enterococcus faecalis, Enterococcus faecium, Escherichia coli, Haemophilus influenzae, Helicobacter pylori, Histoplasma capsulatum, Klebsiella pneumoniae, Legionella pneumophila, Listeria monocytogenes, Moraxella catarrhalis, Mycobacterium avium, Mycobacterium bovis, Mycobacterium leprae, Mycobacterium tuberculosis, Mycoplasma genitalium, Mycoplasma pneumoniae, Neisseria gonorrhoeae, Neisseria meningitidis, Nocardia asteroides, Pasteurella haemolytica, Pasteurella multocida, Pneumocystis carinii, Proteus mirabilis, Proteus vulgaris, Pseudomonas aeruginosa, Pseudomonas putida, Pseudomonas syringae, Salmonella bongori, Salmonella cholerasuis, Salmonella enterica, Salmonella paratyphi, Salmonella typhi, Salmonella typhimurium, Shigella boydii, Shigella dysenteriae, Shigella flexneri, Shigella sonnei, Staphylococcus aureus, Staphylococcus epidermidis, Staphylococcus haemolyticus, Streptococcus pneumoniae, Streptococcus mutans, Streptococcus pyogenes, Treponema pallidum, Ureaplasma urealyticum, Vibrio cholerae, Vibrio parahaemolyticus, Vibrio vulnificans, Yersinia enterocolitica, Yersinia pestis* and any species falling within the genera of any of the above species.

172.   The method of Paragraph 168, wherein said test cell is not an *E. coli* cell.

173.   The method of Paragraph 168, wherein said gene product is from an organism other than *E. coli.*

174.   A method for determining the biological pathway on which a test compound acts comprising:

5   (a) providing a sublethal level of an antisense nucleic acid complementary to a proliferation-required nucleic acid in a first cell, wherein the activity or expression of said proliferation-required nucleic acid is inhibited by an antisense nucleic acid comprising a sequence selected from the group consisting of SEQ ID NOs.: 1-6213 and wherein the biological pathway in which said proliferation-required nucleic acid or a protein encoded

10   by said proliferation-required nucleic acid lies is known,

(b) contacting said first cell with said test compound; and

(c) determining the degree to which said test compound inhibits proliferation of said first cell relative to a cell which does not contain said antisense nucleic acid.

175.   The method of Paragraph 174, wherein said determining step comprises

15   determining whether said first cell has a substantially greater sensitivity to said test compound than a cell which does not express said sublethal level of said antisense nucleic acid.

176.   The method of Paragraph 174, further comprising:

(d) providing a sublethal level of a second antisense nucleic acid complementary to a second proliferation-required nucleic acid in a second cell, wherein said second

20   proliferation-required nucleic acid is in a different biological pathway than said proliferation-required nucleic acid in step (a); and

(e) determining whether said second cell does not have a substantially greater sensitivity to said test compound than a cell which does not express said sublethal level of said second antisense nucleic acid, wherein said test compound is specific for the biological

25   pathway against which the antisense nucleic acid of step (a) acts if said first cell has a substantially greater sensitivity to said test compound than said second cell.

177.   The method of Paragraph 174, wherein said first cell is selected from the group consisting of *Acinetobacter baumannii, Anaplasma marginale, Aspergillus fumigatus, Bacillus anthracis, Bacteroides fragilis, Bordetella pertussis, Borrelia burgdorferi, Burkholderia cepacia,*

30   *Burkholderia fungorum, Burkholderia mallei, Campylobacter jejuni, Candida albicans, Candida glabrata* (also called *Torulopsis glabrata*), *Candida tropicalis, Candida parapsilosis, Candida guilliermondii, Candida krusei, Candida kefyr* (also called *Candida pseudotropicalis*), *Candida dubliniensis, Chlamydia pneumoniae, Chlamydia trachomatis, Clostridium acetobutylicum, Clostridium botulinum, Clostridium difficile, Clostridium perfringens, Coccidioides immitis,*

35   *Corynebacterium diptheriae, Cryptococcus neoformans, Enterobacter cloacae, Enterococcus faecalis, Enterococcus faecium, Escherichia coli, Haemophilus influenzae, Helicobacter pylori, Histoplasma capsulatum, Klebsiella pneumoniae, Legionella pneumophila, Listeria monocytogenes, Moraxella catarrhalis, Mycobacterium avium, Mycobacterium bovis,*

Mycobacterium leprae, Mycobacterium tuberculosis, Mycoplasma genitalium, Mycoplasma pneumoniae, Neisseria gonorrhoeae, Neisseria meningitidis, Nocardia asteroides, Pasteurella haemolytica, Pasteurella multocida, Pneumocystis carinii, Proteus mirabilis, Proteus vulgaris, Pseudomonas aeruginosa, Pseudomonas putida, Pseudomonas syringae, Salmonella bongori,

5   *Salmonella cholerasuis, Salmonella enterica, Salmonella paratyphi, Salmonella typhi, Salmonella typhimurium, Shigella boydii, Shigella dysenteriae, Shigella flexneri, Shigella sonnei, Staphylococcus aureus, Staphylococcus epidermidis, Staphylococcus haemolyticus, Streptococcus pneumoniae, Streptococcus mutans, Streptococcus pyogenes, Treponema pallidum, Ureaplasma urealyticum, Vibrio cholerae, Vibrio parahaemolyticus, Vibrio vulnificans, Yersinia enterocolitica,*

10   *Yersinia pestis* and any species falling within the genera of any of the above species.

178.   The method of Paragraph 174, wherein said first cell is not an *E. coli* cell.

179.   The method of Paragraph 174, wherein said proliferation-required nucleic acid is from an organism other than *E. coli*.

180.   A purified or isolated nucleic acid comprising a sequence selected from the group

15   consisting of SEQ ID NOs.: 1-6213.

181.   A compound which interacts with a gene or gene product whose activity or expression is inhibited by an antisense nucleic acid comprising a nucleotide sequence of one of SEQ ID NOs.: 1-6213 to inhibit proliferation.

182.   The compound of Paragraph 181, wherein said gene product is a polypeptide

20   comprising one of SEQ ID NOs.: 42398-78581.

183.   The compound of Paragraph 181, wherein said gene comprises a nucleotide sequence selected from the group consisting of SEQ ID NOS.: 6214-42397.

184.   A compound which interacts with a gene product whose expression is inhibited by an antisense nucleic acid comprising a nucleotide sequence of one of SEQ ID NOs.: 1-6213 to

25   inhibit proliferation.

185.   A method for manufacturing an antibiotic comprising the steps of:

screening one or more candidate compounds to identify a compound that reduces the activity or level of a gene product required for proliferation, said gene product comprising a gene product whose activity or expression is inhibited by an antisense nucleic acid comprising a

30   nucleotide sequence selected from the group consisting of SEQ ID NOs.: 1-6213; and

manufacturing the compound so identified.

186.   The method of Paragraph 185, wherein said screening step comprises performing any one of the methods of Paragraphs 44, 68, 121, 136, 141, and 157.

187.   The method of Paragraph 185, wherein said gene product is a polypeptide

35   comprising one of SEQ ID NOs:42398-78581.

188.   A method for inhibiting proliferation of a cell in a subject comprising administering an effective amount of a compound that reduces the activity or level of a gene product required for proliferation of said cell, said gene product comprising a gene product whose activity or expression

is inhibited by an antisense nucleic acid comprising a nucleotide sequence selected from the group consisting of SEQ ID NOs.: 1-6213 to said subject.

189.   The method of Paragraph 188 wherein said subject is selected from the group consisting of vertebrates, mammals, avians, and human beings.

190.   The method of Paragraph 188, wherein said gene product comprises a polypeptide comprising an amino acid sequence selected from the group consisting of SEQ ID NOs.: 42398-78581.

191.   The method of Paragraph 188, wherein said cell is selected from the group consisting of *Acinetobacter baumannii, Anaplasma marginale, Aspergillus fumigatus, Bacillus anthracis, Bacteroides fragilis, Bordetella pertussis, Borrelia burgdorferi, Burkholderia cepacia, Burkholderia fungorum, Burkholderia mallei, Campylobacter jejuni, Candida albicans, Candida glabrata* (also called *Torulopsis glabrata*), *Candida tropicalis, Candida parapsilosis, Candida guilliermondii, Candida krusei, Candida kefyr* (also called *Candida pseudotropicalis*), *Candida dubliniensis, Chlamydia pneumoniae, Chlamydia trachomatis, Clostridium acetobutylicum, Clostridium botulinum, Clostridium difficile, Clostridium perfringens, Coccidioides immitis, Corynebacterium diptheriae, Cryptococcus neoformans, Enterobacter cloacae, Enterococcus faecalis, Enterococcus faecium, Escherichia coli, Haemophilus influenzae, Helicobacter pylori, Histoplasma capsulatum, Klebsiella pneumoniae, Legionella pneumophila, Listeria monocytogenes, Moraxella catarrhalis, Mycobacterium avium, Mycobacterium bovis, Mycobacterium leprae, Mycobacterium tuberculosis, Mycoplasma genitalium, Mycoplasma pneumoniae, Neisseria gonorrhoeae, Neisseria meningitidis, Nocardia asteroides, Pasteurella haemolytica, Pasteurella multocida, Pneumocystis carinii, Proteus mirabilis, Proteus vulgaris, Pseudomonas aeruginosa, Pseudomonas putida, Pseudomonas syringae, Salmonella bongori, Salmonella cholerasuis, Salmonella enterica, Salmonella paratyphi, Salmonella typhi, Salmonella typhimurium, Shigella boydii, Shigella dysenteriae, Shigella flexneri, Shigella sonnei, Staphylococcus aureus, Staphylococcus epidermidis, Staphylococcus haemolyticus, Streptococcus pneumoniae, Streptococcus mutans, Streptococcus pyogenes, Treponema pallidum, Ureaplasma urealyticum, Vibrio cholerae, Vibrio parahaemolyticus, Vibrio vulnificans, Yersinia enterocolitica, Yersinia pestis* and any species falling within the genera of any of the above species.

192.   The method of Paragraph 188, wherein said cell is not *E. coli*.

193.   The method of Paragraph 188, wherein said gene product is from an organism other than *E. coli*.

194.   A purified or isolated nucleic acid consisting essentially of the coding sequence of one of SEQ ID NOs: 6214-42397.

195.   A fragment of the nucleic acid of Paragraph 8, said fragment comprising at least 10, at least 20, at least 25, at least 30, at least 50 or more than 50 consecutive nucleotides of one of SEQ ID NOs: 6214-42397.

196.   A purified or isolated nucleic acid comprising a nucleic acid having at least 70% nucleotide sequence identity to a nucleotide sequence selected from the group consisting of SEQ ID NOs.: 6214-42397, fragments comprising at least 25 consecutive nucleotides of SEQ ID NOs.: 6214-42397, the nucleotide sequences complementary to SEQ ID NOs.:6214-42397, and the nucleotide sequences complementary to fragments comprising at least 25 consecutive nucleotides of SEQ ID NOs.: 6214-42397 as determined using BLASTN version 2.0 with the default parameters.

197.   The nucleic acid of Paragraph 196, wherein said nucleic acid is from an organism selected from the group consisting of *Acinetobacter baumannii, Anaplasma marginale, Aspergillus fumigatus, Bacillus anthracis, Bacteroides fragilis, Bordetella pertussis, Borrelia burgdorferi, Burkholderia cepacia, Burkholderia fungorum, Burkholderia mallei, Campylobacter jejuni, Candida albicans, Candida glabrata* (also called *Torulopsis glabrata*), *Candida tropicalis, Candida parapsilosis, Candida guilliermondii, Candida krusei, Candida kefyr* (also called *Candida pseudotropicalis*), *Candida dubliniensis, Chlamydia pneumoniae, Chlamydia trachomatis, Clostridium acetobutylicum, Clostridium botulinum, Clostridium difficile, Clostridium perfringens, Coccidioides immitis, Corynebacterium diptheriae, Cryptococcus neoformans, Enterobacter cloacae, Enterococcus faecalis, Enterococcus faecium, Escherichia coli, Haemophilus influenzae, Helicobacter pylori, Histoplasma capsulatum, Klebsiella pneumoniae, Legionella pneumophila, Listeria monocytogenes, Moraxella catarrhalis, Mycobacterium avium, Mycobacterium bovis, Mycobacterium leprae, Mycobacterium tuberculosis, Mycoplasma genitalium, Mycoplasma pneumoniae, Neisseria gonorrhoeae, Neisseria meningitidis, Nocardia asteroides, Pasteurella haemolytica, Pasteurella multocida, Pneumocystis carinii, Proteus mirabilis, Proteus vulgaris, Pseudomonas aeruginosa, Pseudomonas putida, Pseudomonas syringae, Salmonella bongori, Salmonella cholerasuis, Salmonella enterica, Salmonella paratyphi, Salmonella typhi, Salmonella typhimurium, Shigella boydii, Shigella dysenteriae, Shigella flexneri, Shigella sonnei, Staphylococcus aureus, Staphylococcus epidermidis, Staphylococcus haemolyticus, Streptococcus pneumoniae, Streptococcus mutans, Streptococcus pyogenes, Treponema pallidum, Ureaplasma urealyticum, Vibrio cholerae, Vibrio parahaemolyticus, Vibrio vulnificans, Yersinia enterocolitica, Yersinia pestis* and any species falling within the genera of any of the above species.

198.   The nucleic acid of Paragraph 196, wherein said nucleic acid is from an organism other than *E. coli*.

199.   A method of inhibiting proliferation of a cell comprising inhibiting the activity or reducing the amount of a gene product in said cell or inhibiting the activity or reducing the amount of a nucleic acid encoding said gene product in said cell, wherein said gene product is selected from the group consisting of a gene product having having at least 70% nucleotide sequence identity as determined using BLASTN version 2.0 with the default parameters to a gene product whose expression is inhibited by an antisense nucleic acid comprising a nucleotide sequence selected from the group consisting of SEQ ID NOs.: 1-6213, a gene product encoded by a nucleic acid having at

least 70% nucleotide sequence identity as determined using BLASTN version 2.0 with the default parameters to a nucleic acid encoding a gene product whose expression is inhibited by an antisense nucleic acid comprising a nucleotide sequence selected from the group consisting of SEQ ID NOs:1-6213, a gene product having at least 25% amino acid identity as determined using FASTA

5   version 3.0t78 with the default parameters to a gene product whose expression is inhibited by an antisense nucleic acid comprising a nucleotide sequence selected from the group consisting of SEQ ID NOs.: 1-6213, a gene product encoded by a nucleic acid which hybridizes to a nucleic acid comprising a nucleotide sequence selected from the group consisting of SEQ ID NOs.: 1-6213 under stringent conditions, a gene product encoded by a nucleic acid which hybridizes to a nucleic

10   acid comprising a nucleotide sequence selected from the group consisting of SEQ ID NOs.: 1-6213 under moderate conditions, and a gene product whose activity may be complemented by the gene product whose activity is inhibited by a nucleic acid comprising a nucleotide sequence selected from the group consisting of SEQ ID NOs: 1-6213.

200.   The method of Paragraph 199, wherein said method comprises inhibiting said

15   activity or reducing said amount of said gene product or inhibiting the activity or reducing the amount of a nucleic acid encoding said gene product in an organism selected from the group consisting of *Acinetobacter baumannii, Anaplasma marginale, Aspergillus fumigatus, Bacillus anthracis, Bacteroides fragilis, Bordetella pertussis, Borrelia burgdorferi, Burkholderia cepacia, Burkholderia fungorum, Burkholderia mallei, Campylobacter jejuni, Candida albicans, Candida*

20   *glabrata* (also called *Torulopsis glabrata*), *Candida tropicalis, Candida parapsilosis, Candida guilliermondii, Candida krusei, Candida kefyr* (also called *Candida pseudotropicalis*), *Candida dubliniensis, Chlamydia pneumoniae, Chlamydia trachomatis, Clostridium acetobutylicum, Clostridium botulinum, Clostridium difficile, Clostridium perfringens, Coccidioides immitis, Corynebacterium diptheriae, Cryptococcus neoformans, Enterobacter cloacae, Enterococcus*

25   *faecalis, Enterococcus faecium, Escherichia coli, Haemophilus influenzae, Helicobacter pylori, Histoplasma capsulatum, Klebsiella pneumoniae, Legionella pneumophila, Listeria monocytogenes, Moraxella catarrhalis, Mycobacterium avium, Mycobacterium bovis, Mycobacterium leprae, Mycobacterium tuberculosis, Mycoplasma genitalium, Mycoplasma pneumoniae, Neisseria gonorrhoeae, Neisseria meningitidis, Nocardia asteroides, Pasteurella*

30   *haemolytica, Pasteurella multocida, Pneumocystis carinii, Proteus mirabilis, Proteus vulgaris, Pseudomonas aeruginosa, Pseudomonas putida, Pseudomonas syringae, Salmonella bongori, Salmonella cholerasuis, Salmonella enterica, Salmonella paratyphi, Salmonella typhi, Salmonella typhimurium, Shigella boydii, Shigella dysenteriae, Shigella flexneri, Shigella sonnei, Staphylococcus aureus, Staphylococcus epidermidis, Staphylococcus haemolyticus, Streptococcus*

35   *pneumoniae, Streptococcus mutans, Streptococcus pyogenes, Treponema pallidum, Ureaplasma urealyticum, Vibrio cholerae, Vibrio parahaemolyticus, Vibrio vulnificans, Yersinia enterocolitica, Yersinia pestis* and any species falling within the genera of any of the above species.

201.   The method of Paragraph 199, wherein said method comprises inhibiting said activity or reducing said amount of said gene product or inhibiting the activity or reducing the amount of a nucleic acid encoding said gene product in an organism other than *E. coli.*

202.   The method of Paragraph 199, wherein said gene product is from an organism other than *E. coli.*

203.   The method of Paragraph 199, wherein said gene product comprises a polypeptide selected from the group consisting of a polypeptide having at least 25% amino acid identity as determined using FASTA version 3.0t78 to a polypeptide selected from the group consisting of SEQ ID NOs.: 42398-78581 and a polypeptide whose activity may be complemented by a polypeptide selected from the group consisting of SEQ ID NOs: 42398-78581.

204.   The method of Paragraph 199, wherein said gene product is encoded by a nucleic acid selected from the group consisting of a nucleic acid comprising a nucleic acid having at least 70% nucleotide sequence identity as determined using BLASTN version 2.0 with the default parameters to a nucleotide sequence selected from the group consisting of SEQ ID NOS.: 6214-42397, a nucleic acid comprising a nucleotide sequence which hybridizes to a sequence selected from the group consisting of SEQ ID NOS.: 6214-42397 under stringent conditions, and a nucleic acid comprising a nucloetide sequence which hybridizes to a nucleotide sequence selected from the group consisting of SEQ ID NOS.: 6214-42397 under moderate condtions.

205.   A method for identifying a compound which influences the activity of a gene product required for proliferation comprising:

contacting a candidate compound with a gene product selected from the group consisting of a gene product having at least 70% nucleotide sequence identity as determined using BLASTN version 2.0 with the default parameters to a gene product whose expression is inhibited by an antisense nucleic acid comprising a nucleotide sequence selected from the group consisting of SEQ ID NOs.: 1-6213, a gene product encoded by a nucleic acid having at least 70% nucleotide sequence identity as determined using BLASTN version 2.0 with the default parameters to a nucleic acid encoding a gene product whose expression is inhibited by an antisense nucleic acid comprising a nucleotide sequence selected from the group consisting of SEQ ID NOs:1-6213, a gene product having at least 25% amino acid identity as determined using FASTA version 3.0t78 with the default parameters to a gene product whose expression is inhibited by an antisense nucleic acid comprising a nucleotide sequence selected from the group consisting of SEQ ID NOs.: 1-6213, a gene product encoded by a nucleic acid comprising a nucleotide sequence which hybridizes to a nucleic acid selected from the group consisting of SEQ ID NOs.: 1-6213 under stringent conditions, a gene product encoded by a nucleic acid comprising a nucleotide sequence which hybridizes to a nucleic acid selected from the group consisting of SEQ ID NOs.: 1-6213 under moderate conditions, and a gene product whose activity may be complemented

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by the gene product whose activity is inhibited by a nucleic acid selected from the group consisting of SEQ ID NOs: 1-6213; and

determining whether said candidate compound influences the activity of said gene product.

5   206.   The method of Paragraph 205, wherein said gene product is from an organism selected from the group consisting of *Acinetobacter baumannii, Anaplasma marginale, Aspergillus fumigatus, Bacillus anthracis, Bacteroides fragilis, Bordetella pertussis, Borrelia burgdorferi, Burkholderia cepacia, Burkholderia fungorum, Burkholderia mallei, Campylobacter jejuni, Candida albicans, Candida glabrata* (also called *Torulopsis glabrata*), *Candida tropicalis, Candida*

10   *parapsilosis, Candida guilliermondii, Candida krusei, Candida kefyr* (also called *Candida pseudotropicalis*), *Candida dubliniensis, Chlamydia pneumoniae, Chlamydia trachomatis, Clostridium acetobutylicum, Clostridium botulinum, Clostridium difficile, Clostridium perfringens, Coccidioides immitis, Corynebacterium diptheriae, Cryptococcus neoformans, Enterobacter cloacae, Enterococcus faecalis, Enterococcus faecium, Escherichia coli, Haemophilus influenzae,*

15   *Helicobacter pylori, Histoplasma capsulatum, Klebsiella pneumoniae, Legionella pneumophila, Listeria monocytogenes, Moraxella catarrhalis, Mycobacterium avium, Mycobacterium bovis, Mycobacterium leprae, Mycobacterium tuberculosis, Mycoplasma genitalium, Mycoplasma pneumoniae, Neisseria gonorrhoeae, Neisseria meningitidis, Nocardia asteroides, Pasteurella haemolytica, Pasteurella multocida, Pneumocystis carinii, Proteus mirabilis, Proteus vulgaris,*

20   *Pseudomonas aeruginosa, Pseudomonas putida, Pseudomonas syringae, Salmonella bongori, Salmonella cholerasuis, Salmonella enterica, Salmonella paratyphi, Salmonella typhi, Salmonella typhimurium, Shigella boydii, Shigella dysenteriae, Shigella flexneri, Shigella sonnei, Staphylococcus aureus, Staphylococcus epidermidis, Staphylococcus haemolyticus, Streptococcus pneumoniae, Streptococcus mutans, Streptococcus pyogenes, Treponema pallidum, Ureaplasma*

25   *urealyticum, Vibrio cholerae, Vibrio parahaemolyticus, Vibrio vulnificans, Yersinia enterocolitica, Yersinia pestis* and any species falling within the genera of any of the above species.

207.   The method of Paragraph 205, wherein said gene product is from an organism other than *E. coli*.

208.   The method of Paragraph 205, wherein said gene product is a polypeptide selected

30   from the group consisting of a polypeptide having at least 25% amino acid identity as determined using FASTA version 3.0t78 to a polypeptide selected from the group consisting of SEQ ID NOs.: 42398-78581 and a polypeptide whose activity may be complemented by a polypeptide selected . from the group consisting of SEQ ID NOs: 42398-78581.

209.   The method of Paragraph 205, wherein said gene product is encoded by a nucleic

35   acid selected from the group consisting of a nucleic acid comprising a nucleic acid having at least 70% nucleotide sequence identity as determined using BLASTN version 2.0 with the default parameters to a nucleotide sequence selected from the group consisting of SEQ ID NOS.: 6214-42397, a nucleic acid which hybridizes to a sequence selected from the group consisting of SEQ ID

NOS.: 6214-42397 under stringent conditions, and a nucleic acid which hybridizes to a sequence selected from the group consisting of SEQ ID NOS.: 6214-42397 under moderate condtions.

210.   A compound identified using the method of Paragraph 205.

211.   A method for identifying a compound or nucleic acid having the ability to reduce
5   the activity or level of a gene product required for proliferation comprising:

(a) providing a target that is a gene or RNA, wherein said target comprises a nucleic acid that encodes a gene product selected from the group consisting of a gene product having having at least 70% nucleotide sequence identity as determined using BLASTN version 2.0 with the default parameters to a gene product whose expression is
10   inhibited by an antisense nucleic acid comprising a nucleotide sequence selected from the group consisting of SEQ ID NOs.: 1-6213, a gene product encoded by a nucleic acid having at least 70% nucleic acid identity as determined using BLASTN version 2.0 with the default parameters to a nucleic acid encoding a gene product whose expression is inhibited by an antisense nucleic acid comprising a nucleotide sequence selected from the group
15   consisting of SEQ ID NOs:1-6213, a gene product having at least 25% amino acid identity as determined using FASTA version 3.0t78 with the default parameters to a gene product whose expression is inhibited by an antisense nucleic acid comprising a sequence selected from the group consisting of SEQ ID NOs.: 1-6213, a gene product encoded by a nucleic acid comprising a nucleotide sequence which hybridizes to a nucleic acid selected from the
20   group consisting of SEQ ID NOs.: 1-6213 under stringent conditions, a gene product encoded by a nucleic acid comprising a nucleotide sequence which hybridizes to a nucleic acid selected from the group consisting of SEQ ID NOs.: 1-6213 under moderate conditions, and a gene product whose activity may be complemented by the gene product whose activity is inhibited by a nucleic acid selected from the group consisting of SEQ ID
25   NOs: 1-6213;

(b) contacting said target with a candidate compound or nucleic acid; and

(c) measuring an activity of said target.

212.   The method of Paragraph 211, wherein said target gene or RNA is from an organism selected from the group consisting of *Acinetobacter baumannii, Anaplasma marginale,*
30   *Aspergillus fumigatus, Bacillus anthracis, Bacteroides fragilis, Bordetella pertussis, Borrelia burgdorferi, Burkholderia cepacia, Burkholderia fungorum, Burkholderia mallei, Campylobacter jejuni, Candida albicans, Candida glabrata* (also called *Torulopsis glabrata*), *Candida tropicalis, Candida parapsilosis, Candida guilliermondii, Candida krusei, Candida kefyr* (also called *Candida pseudotropicalis*), *Candida dubliniensis, Chlamydia pneumoniae, Chlamydia trachomatis,*
35   *Clostridium acetobutylicum, Clostridium botulinum, Clostridium difficile, Clostridium perfringens, Coccidioides immitis, Corynebacterium diptheriae, Cryptococcus neoformans, Enterobacter cloacae, Enterococcus faecalis, Enterococcus faecium, Escherichia coli, Haemophilus influenzae, Helicobacter pylori, Histoplasma capsulatum, Klebsiella pneumoniae, Legionella pneumophila,*

Listeria monocytogenes, Moraxella catarrhalis, Mycobacterium avium, Mycobacterium bovis, Mycobacterium leprae, Mycobacterium tuberculosis, Mycoplasma genitalium, Mycoplasma pneumoniae, Neisseria gonorrhoeae, Neisseria meningitidis, Nocardia asteroides, Pasteurella haemolytica, Pasteurella multocida, Pneumocystis carinii, Proteus mirabilis, Proteus vulgaris,

5   *Pseudomonas aeruginosa, Pseudomonas putida, Pseudomonas syringae, Salmonella bongori, Salmonella cholerasuis, Salmonella enterica, Salmonella paratyphi, Salmonella typhi, Salmonella typhimurium, Shigella boydii, Shigella dysenteriae, Shigella flexneri, Shigella sonnei, Staphylococcus aureus, Staphylococcus epidermidis, Staphylococcus haemolyticus, Streptococcus pneumoniae, Streptococcus mutans, Streptococcus pyogenes, Treponema pallidum, Ureaplasma*

10 *urealyticum, Vibrio cholerae, Vibrio parahaemolyticus, Vibrio vulnificans, Yersinia enterocolitica, Yersinia pestis* and any species falling within the genera of any of the above species.

213.   The method of Paragraph 211, wherein said target gene or RNA is from an organism other than *E. coli.*

214.   The method of Paragraph 211, wherein said gene product is from an organism other

15 than *E. coli.*

215.   The method of Paragraph 211, wherein said target is a messenger RNA molecule and said activity is translation of said messenger RNA.

216.   The method of Paragraph 211, wherein said compound is a nucleic acid and said activity is translation of said gene product.

20 217.   The method of Paragraph 211, wherein said target is a gene and said activity is transcription of said gene.

218.   The method of Paragraph 211, wherein said target is a nontranslated RNA and said activity is processing or folding of said nontranslated RNA or assembly of said nontranslated RNA into a protein/RNA complex.

25 219.   The method of Paragraph 211, wherein said target gene is a messenger RNA molecule encoding a polypeptide selected from the group consisting of a polypeptide having at least 25% amino acid identity as determined using FASTA version 3.0t78 to a polypeptide selected from the group consisting of SEQ ID NOs.: 42398-78581 and a polypeptide whose activity may be complemented by a polypeptide selected from the group consisting of SEQ ID NOs: 42398-78581.

30 220.   The method of Paragraph 11, wherein said target gene comprises a nucleic acid selected from the group consisting of a nucleic acid comprising a nucleic acid having at least 70% nucleotide sequence identity as determined using BLASTN version 2.0 with the default parameters to a nucleotide sequence selected from the group consisting of SEQ ID NOS.: 6214-42397, a nucleic acid which hybridizes to a sequence selected from the group consisting of SEQ ID NOS.:

35 6214-42397 under stringent conditions, and a nucleic acid which hybridizes to a sequence selected from the group consisting of SEQ ID NOS.: 6214-42397 under moderate condtions.

221.   A compound or nucleic acid identified using the method of Paragraph 211.

222.   A method for identifying a compound which reduces the activity or level of a gene product required for proliferation of a cell comprising:

(a) providing a sublethal level of an antisense nucleic acid complementary to a nucleic acid encoding said gene product in a cell to reduce the activity or amount of said gene product in said cell, thereby producing a sensitized cell, wherein said gene product is selected from the group consisting of a gene product having having at least 70% nucleic acid identity as determined using BLASTN version 2.0 with the default parameters to a gene product whose expression is inhibited by an antisense nucleic acid comprising a nucleotide sequence selected from the group consisting of SEQ ID NOs.: 1-6213, a gene product encoded by a nucleic acid having at least 70% nucleotide sequence identity as determined using BLASTN version 2.0 with the default parameters to a nucleic acid encoding a gene product whose expression is inhibited by an antisense nucleic acid comprising a nucleotide sequence selected from the group consisting of SEQ ID NOs:1-6213, a gene product having at least 25% amino acid identity as determined using FASTA version 3.0t78 with the default parameters to a gene product whose expression is inhibited by an antisense nucleic acid comprising a nucleotide sequence selected from the group consisting of SEQ ID NOs.: 1-6213, a gene product encoded by a nucleic acid comprising a nucleotide sequence which hybridizes to a nucleic acid selected from the group consisting of SEQ ID NOs.: 1-6213 under stringent conditions, a gene product encoded by a nucleic acid comprising a nucleotide sequence which hybridizes to a nucleic acid comprising a nucleotide sequence selected from the group consisting of SEQ ID NOs.: 1-6213 under moderate conditions, and a gene product whose activity may be complemented by the gene product whose activity is inhibited by a nucleic acid selected from the group consisting of SEQ ID NOs: 1-6213;

(b) contacting said sensitized cell with a compound; and

(c) determining the degree to which said compound inhibits the growth of said sensitized cell relative to a cell which does not contain said antisense nucleic acid.

223.   The method of Paragraph 222, wherein said determining step comprises determining whether said compound inhibits the growth of said sensitized cell to a greater extent than said compound inhibits the growth of a nonsensitized cell.

224.   The method of Paragraph 222, wherein said sensitized cell is a Gram positive bacterium.

225.   The method of Paragraph 224, wherein said Gram positive bacterium is selected from the group consisting of *Staphylococcus* species, *Streptococcus* species, *Enterococcus* species, *Mycobacterium* species, *Clostridium* species, and *Bacillus* species.

226.   The method of Paragraph 225, wherein said bacterium is *Staphylococcus aureus*.

227.   The method of Paragraph 224, wherein said *Staphylococcus* species is coagulase negative.

228.   The method of Paragraph 226, wherein said bacterium is selected from the group consisting of *Staphylococcus aureus* RN450 and *Staphylococcus aureus* RN4220.

229.   The method of Paragraph 222, wherein said sensitized cell is an organism selected from the group consisting of *Acinetobacter baumannii, Anaplasma marginale, Aspergillus fumigatus, Bacillus anthracis, Bacteroides fragilis, Bordetella pertussis, Borrelia burgdorferi, Burkholderia cepacia, Burkholderia fungorum, Burkholderia mallei, Campylobacter jejuni, Candida albicans, Candida glabrata* (also called *Torulopsis glabrata*), *Candida tropicalis, Candida parapsilosis, Candida guilliermondii, Candida krusei, Candida kefyr* (also called *Candida pseudotropicalis*), *Candida dubliniensis, Chlamydia pneumoniae, Chlamydia trachomatis, Clostridium acetobutylicum, Clostridium botulinum, Clostridium difficile, Clostridium perfringens, Coccidioides immitis, Corynebacterium diptheriae, Cryptococcus neoformans, Enterobacter cloacae, Enterococcus faecalis, Enterococcus faecium, Escherichia coli, Haemophilus influenzae, Helicobacter pylori, Histoplasma capsulatum, Klebsiella pneumoniae, Legionella pneumophila, Listeria monocytogenes, Moraxella catarrhalis, Mycobacterium avium, Mycobacterium bovis, Mycobacterium leprae, Mycobacterium tuberculosis, Mycoplasma genitalium, Mycoplasma pneumoniae, Neisseria gonorrhoeae, Neisseria meningitidis, Nocardia asteroides, Pasteurella haemolytica, Pasteurella multocida, Pneumocystis carinii, Proteus mirabilis, Proteus vulgaris, Pseudomonas aeruginosa, Pseudomonas putida, Pseudomonas syringae, Salmonella bongori, Salmonella cholerasuis, Salmonella enterica, Salmonella paratyphi, Salmonella typhi, Salmonella typhimurium, Shigella boydii, Shigella dysenteriae, Shigella flexneri, Shigella sonnei, Staphylococcus aureus, Staphylococcus epidermidis, Staphylococcus haemolyticus, Streptococcus pneumoniae, Streptococcus mutans, Streptococcus pyogenes, Treponema pallidum, Ureaplasma urealyticum, Vibrio cholerae, Vibrio parahaemolyticus, Vibrio vulnificans, Yersinia enterocolitica, Yersinia pestis* and any species falling within the genera of any of the above species.

230.   The method of Paragraph 222, wherein said cell is an organism other than *E. coli*.

231.   The method of Paragraph 222, wherein said gene product is from an organism other than *E. coli*.

232.   The method of Paragraph 222, wherein said antisense nucleic acid is transcribed from an inducible promoter.

233.   The method of Paragraph 222, further comprising the step of contacting said cell with a concentration of inducer which induces transcription of said antisense nucleic acid to a sublethal level.

234.   The method of Paragraph 222, wherein growth inhibition is measured by monitoring optical density of a culture medium.

235.   The method of Paragraph 222, wherein said gene product is a polypeptide.

236.   The method of Paragraph 235, wherein said polypeptide comprises a polypeptide selected from the group consisting of a polypeptide having at least 25% amino acid identity as determined using FASTA version 3.0t78 to a polypeptide selected from the group consisting of

SEQ ID NOs.: 42398-78581 and a polypeptide whose activity may be complemented by a polypeptide selected from the group consisting of SEQ ID NOs: 42398-78581.

237.   The method of Paragraph 222, wherein said gene product is an RNA.

238.   The method of Paragraph 222, wherein said nucleic acid encoding said gene product comprises a nucleic acid selected from the group consisting of a nucleic acid comprising a nucleic acid having at least 70% nucleic acid identity as determined using BLASTN version 2.0 with the default parameters to a sequence selected from the group consisting of SEQ ID NOS.: 6214-42397, a nucleic acid which hybridizes to a sequence selected from the group consisting of SEQ ID NOS.: 6214-42397 under stringent conditions, and a nucleic acid which hybridizes to a sequence selected from the group consisting of SEQ ID NOS.: 6214-42397 under moderate condtions.

239.   A compound identified using the method of Paragraph 222.

240.   A method for inhibiting cellular proliferation comprising introducing a compound with activity against a gene product or a compound with activity against a gene encoding said gene product into a population of cells expressing said gene product, wherein said gene product is selected from the group consisting of a gene product having at least 70% nucleotide sequence identity as determined using BLASTN version 2.0 with the default parameters to a gene product whose expression is inhibited by an antisense nucleic acid comprising a nucleotide sequence selected from the group consisting of SEQ ID NOs.: 1-6213, a gene product encoded by a nucleic acid having at least 70% nucleotide sequence identity as determined using BLASTN version 2.0 with the default parameters to a nucleic acid encoding a gene product whose expression is inhibited by an antisense nucleic acid comprising a nucleotide sequence selected from the group consisting of SEQ ID NOs:1-6213, a gene product having at least 25% amino acid identity as determined using FASTA version 3.0t78 with the default parameters to a gene product whose expression is inhibited by an antisense nucleic acid comprising a nucleotide sequence selected from the group consisting of SEQ ID NOs.: 1-6213, a gene product encoded by a nucleic acid comprising a nucleotide sequence which hybridizes to a nucleic acid selected from the group consisting of SEQ ID NOs.: 1-6213 under stringent conditions, a gene product encoded by a nucleic acid comprising a nucleotide sequence which hybridizes to a nucleic acid selected from the group consisting of SEQ ID NOs.: 1-6213 under moderate conditions, and a gene product whose activity may be complemented by the gene product whose activity is inhibited by a nucleic acid selected from the group consisting of SEQ ID NOs: 1-6213.

241.   The method of Paragraph 240, wherein said compound is an antisense nucleic acid comprising a nucleotide sequence selected from the group consisting of SEQ ID NOs.: 1-6213, or a proliferation-inhibiting portion thereof.

242.   The method of Paragraph 240, wherein said proliferation inhibiting portion of one of SEQ ID NOs.: 1-6213 is a fragment comprising at least 10, at least 20, at least 25, at least 30, at least 50 or more than 51 consecutive nucleotides of one of SEQ ID NOs.: 1-6213.

243.   The method of Paragraph 240, wherein said population is a population of Gram positive bacteria.

244.   The method of Paragraph 243, wherein said population of Gram positive bacteria is selected from the group consisting of a population of *Staphylococcus* species, *Streptococcus* species, *Enterococcus* species, *Mycobacterium* species, *Clostridium* species, and *Bacillus* species.

245.   The method of Paragraph 243, wherein said population is a population of *Staphylococcus aureus*.

246.   The method of Paragraph 245, wherein said population is a population of a bacterium selected from the group consisting of *Staphylococcus aureus* RN450 and *Staphylococcus aureus* RN4220.

247.   The method of Paragraph 240, wherein said population is a population of a bacterium selected from the group consisting of *Acinetobacter baumannii, Anaplasma marginale, Aspergillus fumigatus, Bacillus anthracis, Bacteroides fragilis, Bordetella pertussis, Borrelia burgdorferi, Burkholderia cepacia, Burkholderia fungorum, Burkholderia mallei, Campylobacter jejuni, Candida albicans, Candida glabrata* (also called *Torulopsis glabrata*), *Candida tropicalis, Candida parapsilosis, Candida guilliermondii, Candida krusei, Candida kefyr* (also called *Candida pseudotropicalis*), *Candida dubliniensis, Chlamydia pneumoniae, Chlamydia trachomatis, Clostridium acetobutylicum, Clostridium botulinum, Clostridium difficile, Clostridium perfringens, Coccidioides immitis, Corynebacterium diptheriae, Cryptococcus neoformans, Enterobacter cloacae, Enterococcus faecalis, Enterococcus faecium, Escherichia coli, Haemophilus influenzae, Helicobacter pylori, Histoplasma capsulatum, Klebsiella pneumoniae, Legionella pneumophila, Listeria monocytogenes, Moraxella catarrhalis, Mycobacterium avium, Mycobacterium bovis, Mycobacterium leprae, Mycobacterium tuberculosis, Mycoplasma genitalium, Mycoplasma pneumoniae, Neisseria gonorrhoeae, Neisseria meningitidis, Nocardia asteroides, Pasteurella haemolytica, Pasteurella multocida, Pneumocystis carinii, Proteus mirabilis, Proteus vulgaris, Pseudomonas aeruginosa, Pseudomonas putida, Pseudomonas syringae, Salmonella bongori, Salmonella cholerasuis, Salmonella enterica, Salmonella paratyphi, Salmonella typhi, Salmonella typhimurium, Shigella boydii, Shigella dysenteriae, Shigella flexneri, Shigella sonnei, Staphylococcus aureus, Staphylococcus epidermidis, Staphylococcus haemolyticus, Streptococcus pneumoniae, Streptococcus mutans, Streptococcus pyogenes, Treponema pallidum, Ureaplasma urealyticum, Vibrio cholerae, Vibrio parahaemolyticus, Vibrio vulnificans, Yersinia enterocolitica, Yersinia pestis* and any species falling within the genera of any of the above species.

248.   The method of Paragraph 240, wherein said population is a population of an organism other than *E. coli*.

249.   The method of Paragraph 240, wherein said product of said gene is from an organism other than *E. coli*.

250.   The method of Paragraph 240, wherein said gene product is selected from the group consisting of a polypeptide having at least 25% amino acid identity as determined using

FASTA version 3.0t78 to a polypeptide selected from the group consisting of SEQ ID NOs.: 42398-78581 and a polypeptide whose activity may be complemented by a polypeptide selected from the group consisting of SEQ ID NOs: 42398-78581.

251.   The method of Paragraph 240, wherein said gene comprises a nucleic acid selected from the group consisting of a nucleic acid comprising a nucleic acid having at least 70% nucleotide sequence identity as determined using BLASTN version 2.0 with the default parameters to a nucleotide sequence selected from the group consisting of SEQ ID NOS.: 6214-42397, a nucleic acid comprising a nucleotide sequence which hybridizes to a nucleotide sequence selected from the group consisting of SEQ ID NOS.: 6214-42397 under stringent conditions, and a nucleic acid comprising a nucleotide sequence which hybridizes to a nucleotide sequence selected from the group consisting of SEQ ID NOS.: 6214-42397 under moderate condtions.

252.   A preparation comprising an effective concentration of an antisense nucleic acid in a pharmaceutically acceptable carrier wherein said antisense nucleic acid is selected from the group consisting of a nucleic acid comprising a sequence having at least 70% nucleotide sequence identity as determined using BLASTN version 2.0 with the default parameters to a nucleotide sequence selected from the group consisting of SEQ ID NOs.: 1-6213 or a proliferation-inhibiting portion thereof, a nucleic acid comprising a nucleotide sequence which hybridizes to a nucleic acid selected from the group consisting of SEQ ID NOs.: 1-6213 under stringent conditions, and a nucleic acid comprising a nucleotide sequence which hybridizes to a nucleic acid selected from the group consisting of SEQ ID NOs.: 1-6213 under moderate conditions.

253.   The preparation of Paragraph 252, wherein said proliferation-inhibiting portion of one of SEQ ID NOs.: 1-6213 comprises at least 10, at least 20, at least 25, at least 30, at least 50 or more than 50 consecutive nucleotides of one of SEQ ID NOs.: 1-6213.

254.   A method for inhibiting the activity or expression of a gene in an operon which encodes a gene product required for proliferation comprising contacting a cell in a cell population with an antisense nucleic acid comprising at least a proliferation-inhibiting portion of said operon in an antisense orientation, wherein said gene product is selected from the group consisting of a gene product having at least 70% nucleotide sequence identity as determined using BLASTN version 2.0 with the default parameters to a gene product whose expression is inhibited by an antisense nucleic acid comprising a nucleotide sequence selected from the group consisting of SEQ ID NOs.: 1-6213, a gene product encoded by a nucleic acid having at least 70% nucleotide sequence identity as determined using BLASTN version 2.0 with the default parameters to a nucleic acid encoding a gene product whose expression is inhibited by an antisense nucleic acid comprising a nucleotide sequence selected from the group consisting of SEQ ID NOs:1-6213, a gene product having at least 25% amino acid identity as determined using FASTA version 3.0t78 with the default parameters to a gene product whose expression is inhibited by an antisense nucleic acid comprising a nucleotide sequence selected from the group consisting of SEQ ID NOs.: 1-6213, a gene product encoded by a nucleic acid comprising a nucleotide sequence which hybridizes to a nucleic acid selected from the

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group consisting of SEQ ID NOs.: 1-6213 under stringent conditions, a gene product encoded by a nucleic acid comprising a nucleotide sequence which hybridizes to a nucleic acid selected from the group consisting of SEQ ID NOs.: 1-6213 under moderate conditions, and a gene product whose activity may be complemented by the gene product whose activity is inhibited by a nucleic acid

5   selected from the group consisting of SEQ ID NOs: 1-6213.

255.   The method of Paragraph 254, wherein said antisense nucleic acid comprises a nucleotide sequence having at least 70% nucleotide sequence identity as determined using BLASTN version 2.0 with the default parameters to a nucleotide seqence selected from the group consisting of SEQ ID NOs.: 1-6213, a proliferation inhibiting portion thereof, a nucleic acid

10   comprising a nucleotide sequence which hybridizes to a nucleic acid selected from the group consisting of SEQ ID NOs.: 1-6213 under stringent conditions, and a nucleic acid which comprising a nucleotide sequence which hybridizes to a nucleic acid selected from the group consisting of SEQ ID NOs.: 1-6213 under moderate conditions.

256.   The method of Paragraph 254, wherein said cell is selected from the group

15   consisting of *Acinetobacter baumannii, Anaplasma marginale, Aspergillus fumigatus, Bacillus anthracis, Bacteroides fragilis, Bordetella pertussis, Borrelia burgdorferi, Burkholderia cepacia, Burkholderia fungorum, Burkholderia mallei, Campylobacter jejuni, Candida albicans, Candida glabrata* (also called *Torulopsis glabrata*), *Candida tropicalis, Candida parapsilosis, Candida guilliermondii, Candida krusei, Candida kefyr* (also called *Candida pseudotropicalis*), *Candida*

20   *dubliniensis, Chlamydia pneumoniae, Chlamydia trachomatis, Clostridium acetobutylicum, Clostridium botulinum, Clostridium difficile, Clostridium perfringens, Coccidioides immitis, Corynebacterium diptheriae, Cryptococcus neoformans, Enterobacter cloacae, Enterococcus faecalis, Enterococcus faecium, Escherichia coli, Haemophilus influenzae, Helicobacter pylori, Histoplasma capsulatum, Klebsiella pneumoniae, Legionella pneumophila, Listeria*

25   *monocytogenes, Moraxella catarrhalis, Mycobacterium avium, Mycobacterium bovis, Mycobacterium leprae, Mycobacterium tuberculosis, Mycoplasma genitalium, Mycoplasma pneumoniae, Neisseria gonorrhoeae, Neisseria meningitidis, Nocardia asteroides, Pasteurella haemolytica, Pasteurella multocida, Pneumocystis carinii, Proteus mirabilis, Proteus vulgaris, Pseudomonas aeruginosa, Pseudomonas putida, Pseudomonas syringae, Salmonella bongori,*

30   *Salmonella cholerasuis, Salmonella enterica, Salmonella paratyphi, Salmonella typhi, Salmonella typhimurium, Shigella boydii, Shigella dysenteriae, Shigella flexneri, Shigella sonnei, Staphylococcus aureus, Staphylococcus epidermidis, Staphylococcus haemolyticus, Streptococcus pneumoniae, Streptococcus mutans, Streptococcus pyogenes, Treponema pallidum, Ureaplasma urealyticum, Vibrio cholerae, Vibrio parahaemolyticus, Vibrio vulnificans, Yersinia enterocolitica,*

35   *Yersinia pestis* and any species falling within the genera of any of the above species.

257.   The method of Paragraph 254, wherein said cell is not an *E. coli* cell.

258.   The method of Paragraph 254, wherein said gene is from an organism other than *E. coli.*

259.   The method of Paragraph 254, wherein said cell is contacted with said antisense nucleic acid by introducing a plasmid which transcribes said antisense nucleic acid into said cell population.

260.   The method of Paragraph 254, wherein said cell is contacted with said antisense nucleic acid by introducing a phage which transcribes said antisense nucleic acid into said cell population.

261.   The method of Paragraph 254, wherein said cell is contacted with said antisense nucleic acid by transcribing said antisense nucleic acid from the chromosome of cells in said cell population.

262.   The method of Paragraph 254, wherein said cell is contacted with said antisense nucleic acid by introducing a promoter adjacent to a chromosomal copy of said antisense nucleic acid such that said promoter directs the synthesis of said antisense nucleic acid.

263.   The method of Paragraph 254, wherein said cell is contacted with said antisense nucleic acid by introducing a retron which expresses said antisense nucleic acid into said cell population.

264.   The method of Paragraph 254, wherein said cell is contacted with said antisense nucleic acid by introducing a ribozyme into said cell-population, wherein a binding portion of said ribozyme is complementary to said antisense oligonucleotide.

265.   The method of Paragraph 254, wherein said cell is contacted with said antisense nucleic acid by introducing a liposome comprising said antisense oligonucleotide into said cell.

266.   The method of Paragraph 254, wherein said cell is contacted with said antisense nucleic acid by electroporation of said antisense nucleic acid into said cell.

267.   The method of Paragraph 254, wherein said antisense nucleic acid has at least 70% nucleotide sequence identity as determined using BLASTN version 2.0 with the default parameters to a nucleotide sequence comprising at least 10, at least 20, at least 25, at least 30, at least 50 or more than 50 consecutive nucleotides of one of SEQ ID NOs.: 1-6213.

268.   The method of Paragraph 254 wherein said antisense nucleic acid is a synthetic oligonucleotide.

269.   The method of Paragraph 254, wherein said gene comprises a nucleic acid selected from the group consisting of a nucleic acid comprising a nucleic acid having at least 70% nucleotide sequence identity as determined using BLASTN version 2.0 with the default parameters to a nucleotide sequence selected from the group consisting of SEQ ID NOS.: 6214-42397, a nucleic acid comprising a nucleotide sequence which hybridizes to a sequence selected from the group consisting of SEQ ID NOS.: 6214-42397 under stringent conditions, and a nucleic acid comprising a nucleotide sequence which hybridizes to a nucleotide sequence selected from the group consisting of SEQ ID NOS.: 6214-42397 under moderate condtions.

270.   A method for identifying a gene which is required for proliferation of a cell comprising:

(a) contacting a cell with an antisense nucleic acid selected from the group consisting of a nucleic acid at least 70% nucleotide sequence identity as determined using BLASTN version 2.0 with the default parameters to a nucleotide sequence selected from the group consisting of SEQ ID NOs.: 1-6213 or a proliferation-inhibiting portion thereof, a nucleic acid comprising a nucleotide sequence which hybridizes to a nucleic acid selected from the group consisting of SEQ ID NOs.: 1-6213 under stringent conditions, and a nucleic acid comprising a nucleotide sequence which hybridizes to a nucleic acid selected from the group consisting of SEQ ID NOs.: 1-6213 under moderate conditions, wherein said cell is a cell other than the organism from which said nucleic acid was obtained;

(b) determining whether said nucleic acid inhibits proliferation of said cell; and

(c) identifying the gene in said cell which encodes the mRNA which is complementary to said antisense nucleic acid or a portion thereof.

271.   The method of Paragraph 270, wherein said cell is selected from the group consisting of *Staphylococcus* species, *Streptococcus* species, *Enterococcus* species, *Mycobacterium* species, *Clostridium* species, and *Bacillus* species.

272.   The method of Paragraph 270 wherein said cell is selected from the group consisting of *Acinetobacter baumannii, Anaplasma marginale, Aspergillus fumigatus, Bacillus anthracis, Bacteroides fragilis, Bordetella pertussis, Borrelia burgdorferi, Burkholderia cepacia, Burkholderia fungorum, Burkholderia mallei, Campylobacter jejuni, Candida albicans, Candida glabrata* (also called *Torulopsis glabrata*), *Candida tropicalis, Candida parapsilosis, Candida guilliermondii, Candida krusei, Candida kefyr* (also called *Candida pseudotropicalis*), *Candida dubliniensis, Chlamydia pneumoniae, Chlamydia trachomatis, Clostridium acetobutylicum, Clostridium botulinum, Clostridium difficile, Clostridium perfringens, Coccidioides immitis, Corynebacterium diptheriae, Cryptococcus neoformans, Enterobacter cloacae, Enterococcus faecalis, Enterococcus faecium, Escherichia coli, Haemophilus influenzae, Helicobacter pylori, Histoplasma capsulatum, Klebsiella pneumoniae, Legionella pneumophila, Listeria monocytogenes, Moraxella catarrhalis, Mycobacterium avium, Mycobacterium bovis, Mycobacterium leprae, Mycobacterium tuberculosis, Mycoplasma genitalium, Mycoplasma pneumoniae, Neisseria gonorrhoeae, Neisseria meningitidis, Nocardia asteroides, Pasteurella haemolytica, Pasteurella multocida, Pneumocystis carinii, Proteus mirabilis, Proteus vulgaris, Pseudomonas aeruginosa, Pseudomonas putida, Pseudomonas syringae, Salmonella bongori, Salmonella cholerasuis, Salmonella enterica, Salmonella paratyphi, Salmonella typhi, Salmonella typhimurium, Shigella boydii, Shigella dysenteriae, Shigella flexneri, Shigella sonnei, Staphylococcus aureus, Staphylococcus epidermidis, Staphylococcus haemolyticus, Streptococcus pneumoniae, Streptococcus mutans, Streptococcus pyogenes, Treponema pallidum, Ureaplasma urealyticum, Vibrio cholerae, Vibrio parahaemolyticus, Vibrio vulnificans, Yersinia enterocolitica, Yersinia pestis* and any species falling within the genera of any of the above species.

273.   The method of Paragraph 270, wherein said cell is not *E. coli*.

274.   The method of Paragraph 270, further comprising operably linking said antisense nucleic acid to a promoter which is functional in said cell, said promoter being included in a vector, and introducing said vector into said cell.

275.   A method for identifying a compound having the ability to inhibit proliferation of a cell comprising:

(a) identifying a homolog of a gene or gene product whose activity or level is inhibited by an antisense nucleic acid in a test cell, wherein said test cell is not the microorgaism from which the antisense nucleic acid was obtained, wherein said antisense nucleic acid is selected from the group consisting of a nucleic acid having at least 70% nucleotide sequence identity as determined using BLASTN version 2.0 with the default parameters to a nucleotide sequence selected from the group consisting of SEQ ID NOs. 1-6213, a nucleic acid comprising a nucleotide sequence which hybridizes to a nucleic acid selected from the group consisting of SEQ ID NOs.: 1-6213 under stringent conditions, and a nucleic acid comprising a nucleotide sequence which hybridizes to a nucleic acid selected from the group consisting of SEQ ID NOs.: 1-6213 under moderate conditions;

(b) identifying an inhibitory nucleic acid sequence which inhibits the activity of said homolog in said test cell;

(c) contacting said test cell with a sublethal level of said inhibitory nucleic acid, thus sensitizing said cell;

(d) contacting the sensitized cell of step (c) with a compound; and

(e) determining the degree to which said compound inhibits proliferation of said sensitized cell relative to a cell which does not express said inhibitory nucleic acid.

276.   The method of Paragraph 275, wherein said determining step comprises determining whether said compound inhibits proliferation of said sensitized test cell to a greater extent than said compound inhibits proliferation of a nonsensitized test cell.

277.   The method of Paragraph 275, wherein step (a) comprises identifying a homologous nucleic acid to a gene or gene product whose activity or level is inhibited by a nucleic acid having at least 70% nucleotide sequence identity as determined using BLASTN version 2.0 with the default parameters to a nucleotide sequence selected from the group consisting of SEQ ID NOs. 1-6213 or a nucleic acid encoding a homologous polypeptide to a polypeptide whose activity or level is inhibited by a nucleic acid having at least 70% nucleotide sequence identity as determined using BLASTN version 2.0 with the default parameters to a nucleotide sequence selected from the group consisting of SEQ ID NOs. 1-6213 by using an algorithm selected from the group consisting of BLASTN version 2.0 with the default parameters and FASTA version 3.0t78 algorithm with the default parameters to identify said homologous nucleic acid or said nucleic acid encoding a homologous polypeptide in a database.

278.   The method of Paragraph 275 wherein said step (a) comprises identifying a homologous nucleic acid or a nucleic acid encoding a homologous polypeptide by identifying

nucleic acids comprising nucleotide sequences which hybridize to said nucleic acid having at least 70% nucleotide sequence identity as determined using BLASTN version 2.0 with the default parameters to a nucleotide sequence selected from the group consisting of SEQ ID NOs. 1-6213 or the complement of the nucleotide sequence of said nucleic acid selected from the group consisting

5   of SEQ ID NOs. 1-6213.

279.   The method of Paragraph 275 wherein step (a) comprises expressing a nucleic acid having at least 70% nucleic acid identity as determined using BLASTN version 2.0 with the default parameters to a sequence selected from the group consisting of SEQ ID NOs. 1-6213 in said test cell.

10   280.   The method of Paragraph 275, wherein step (a) comprises identifying a homologous nucleic acid or a nucleic acid encoding a homologous polypeptide in an test cell selected from the group consisting of *Acinetobacter baumannii*, *Anaplasma marginale*, *Aspergillus fumigatus*, *Bacillus anthracis*, *Bacteroides fragilis*, *Bordetella pertussis*, *Borrelia burgdorferi*, *Burkholderia cepacia*, *Burkholderia fungorum*, *Burkholderia mallei*, *Campylobacter jejuni*,

15   *Candida albicans*, *Candida glabrata* (also called *Torulopsis glabrata*), *Candida tropicalis*, *Candida parapsilosis*, *Candida guilliermondii*, *Candida krusei*, *Candida kefyr* (also called *Candida pseudotropicalis*), *Candida dubliniensis*, *Chlamydia pneumoniae*, *Chlamydia trachomatis*, *Clostridium acetobutylicum*, *Clostridium botulinum*, *Clostridium difficile*, *Clostridium perfringens*, *Coccidioides immitis*, *Corynebacterium diptheriae*, *Cryptococcus neoformans*, *Enterobacter*

20   *cloacae*, *Enterococcus faecalis*, *Enterococcus faecium*, *Escherichia coli*, *Haemophilus influenzae*, *Helicobacter pylori*, *Histoplasma capsulatum*, *Klebsiella pneumoniae*, *Legionella pneumophila*, *Listeria monocytogenes*, *Moraxella catarrhalis*, *Mycobacterium avium*, *Mycobacterium bovis*, *Mycobacterium leprae*, *Mycobacterium tuberculosis*, *Mycoplasma genitalium*, *Mycoplasma pneumoniae*, *Neisseria gonorrhoeae*, *Neisseria meningitidis*, *Nocardia asteroides*, *Pasteurella*

25   *haemolytica*, *Pasteurella multocida*, *Pneumocystis carinii*, *Proteus mirabilis*, *Proteus vulgaris*, *Pseudomonas aeruginosa*, *Pseudomonas putida*, *Pseudomonas syringae*, *Salmonella bongori*, *Salmonella cholerasuis*, *Salmonella enterica*, *Salmonella paratyphi*, *Salmonella typhi*, *Salmonella typhimurium*, *Shigella boydii*, *Shigella dysenteriae*, *Shigella flexneri*, *Shigella sonnei*, *Staphylococcus aureus*, *Staphylococcus epidermidis*, *Staphylococcus haemolyticus*, *Streptococcus*

30   *pneumoniae*, *Streptococcus mutans*, *Streptococcus pyogenes*, *Treponema pallidum*, *Ureaplasma urealyticum*, *Vibrio cholerae*, *Vibrio parahaemolyticus*, *Vibrio vulnificans*, *Yersinia enterocolitica*, *Yersinia pestis* and any species falling within the genera of any of the above species.

281.   The method of Paragraph 275, wherein step (a) comprises identifying a homologous nucleic acid or a nucleic acid encoding a homologous polypeptide in a test cell other

35   than *E. coli*.

282.   The method of Paragraph 275, wherein said inhibitory nucleic acid is an antisense nucleic acid.

283.   The method of Paragraph 275, wherein said inhibitory nucleic acid comprises an antisense nucleic acid to a portion of said homolog.

284.   The method of Paragraph 275, wherein said inhibitory nucleic acid comprises an antisense nucleic acid to a portion of the operon encoding said homolog.

285.   The method of Paragraph 275, wherein the step of contacting the cell with a sublethal level of said inhibitory nucleic acid comprises directly contacting said cell with said inhibitory nucleic acid.

286.   The method of Paragraph 275, wherein the step of contacting the cell with a sublethal level of said inhibitory nucleic acid comprises expressing an antisense nucleic acid to said homolog in said cell.

287.   The method of Paragraph 275, wherein said gene product comprises a polypeptide comprising an amino acid sequence selected from the group consisting of SEQ ID NOs.: 42398-78581.

288.   The method of Paragraph 275, wherein said gene comprises a nucleic acid selected from the group consisting of a nucleic acid comprising a nucleic acid having at least 70% nucleotide sequence identity as determined using BLASTN version 2.0 with the default parameters to a sequence selected from the group consisting of SEQ ID NOS.: 6214-42397, a nucleic acid comprising a nucleotide sequence which hybridizes to a nucleotide sequence selected from the group consisting of SEQ ID NOS.: 6214-42397 under stringent conditions, and a nucleic acid comprising a nucleotide sequence which hybridizes to a nucleotide sequence selected from the group consisting of SEQ ID NOS.: 6214-42397 under moderate condtions.

289.   A compound identified using the method of Paragraph 275.

290.   A method of identifying a compound having the ability to inhibit proliferation comprising:

(a) sensitizing a test cell by contacting said test cell with a sublethal level of an antisense nucleic acid, wherein said antisense nucleic acid is selected from the group consisting of a nucleic acid having at least 70% nucleotide sequence identity as determined using BLASTN version 2.0 with the default parameters to a nucleotide sequence selected from the group consisting of SEQ ID NOs. 1-6213 or a portion thereof which inhibits the proliferation of the cell from which said nucleic acid was obtained, a nucleic acid comprising a nucleotide sequence which hybridizes to a nucleic acid selected from the group consisting of SEQ ID NOs.: 1-6213 under stringent conditions, and a nucleic acid comprising a nucleotide sequence which hybridizes to a nucleic acid selected from the group consisting of SEQ ID NOs.: 1-6213 under moderate conditionst;

(b) contacting the sensitized test cell of step (a) with a compound; and

(c) determining the degree to which said compound inhibits proliferation of said sensitized test cell relative to a cell which does not contain said antisense nucleic acid.

291.   The method of Paragraph 290, wherein said determining step comprises determining whether said compound inhibits proliferation of said sensitized test cell to a greater extent than said compound inhibits proliferation of a nonsensitized test cell.

292.   A compound identified using the method of Paragraph 290.

5   293.   The method of Paragraph 290, wherein said test cell is selected from the group consisting of *Acinetobacter baumannii, Anaplasma marginale, Aspergillus fumigatus, Bacillus anthracis, Bacteroides fragilis, Bordetella pertussis, Borrelia burgdorferi, Burkholderia cepacia, Burkholderia fungorum, Burkholderia mallei, Campylobacter jejuni, Candida albicans, Candida glabrata* (also called *Torulopsis glabrata*), *Candida tropicalis, Candida parapsilosis, Candida*
10   *guilliermondii, Candida krusei, Candida kefyr* (also called *Candida pseudotropicalis*), *Candida dubliniensis, Chlamydia pneumoniae, Chlamydia trachomatis, Clostridium acetobutylicum, Clostridium botulinum, Clostridium difficile, Clostridium perfringens, Coccidioides immitis, Corynebacterium diptheriae, Cryptococcus neoformans, Enterobacter cloacae, Enterococcus faecalis, Enterococcus faecium, Escherichia coli, Haemophilus influenzae, Helicobacter pylori,*
15   *Histoplasma capsulatum, Klebsiella pneumoniae, Legionella pneumophila, Listeria monocytogenes, Moraxella catarrhalis, Mycobacterium avium, Mycobacterium bovis, Mycobacterium leprae, Mycobacterium tuberculosis, Mycoplasma genitalium, Mycoplasma pneumoniae, Neisseria gonorrhoeae, Neisseria meningitidis, Nocardia asteroides, Pasteurella haemolytica, Pasteurella multocida, Pneumocystis carinii, Proteus mirabilis, Proteus vulgaris,*
20   *Pseudomonas aeruginosa, Pseudomonas putida, Pseudomonas syringae, Salmonella bongori, Salmonella cholerasuis, Salmonella enterica, Salmonella paratyphi, Salmonella typhi, Salmonella typhimurium, Shigella boydii, Shigella dysenteriae, Shigella flexneri, Shigella sonnei, Staphylococcus aureus, Staphylococcus epidermidis, Staphylococcus haemolyticus, Streptococcus pneumoniae, Streptococcus mutans, Streptococcus pyogenes, Treponema pallidum, Ureaplasma*
25   *urealyticum, Vibrio cholerae, Vibrio parahaemolyticus, Vibrio vulnificans, Yersinia enterocolitica, Yersinia pestis* and any species falling within the genera of any of the above species.

294.   The method of Paragraph 290, wherein the test cell is not *E. coli.*

295.   . A method for identifying a compound having activity against a biological pathway required for proliferation comprising:

30   (a) sensitizing a cell by providing a sublethal level of an antisense nucleic acid complementary to a nucleic acid encoding a gene product required for proliferation, wherein said gene product is selected from the group consisting of a gene product having at least 70% nucleotide sequence identity as determined using BLASTN version 2.0 with the default parameters to a gene product whose expression is inhibited by an antisense nucleic
35   acid comprising a nucleotide sequence selected from the group consisting of SEQ ID NOs.: 1-6213, a gene product encoded by a nucleic acid having at least 70% nucleotide sequence identity as determined using BLASTN version 2.0 with the default parameters to a nucleic acid encoding a gene product whose expression is inhibited by an antisense nucleic acid

comprising a nucleotide sequence selected from the group consisting of SEQ ID NOs:1-6213, a gene product having at least 25% amino acid identity as determined using FASTA version 3.0t78 with the default parameters to a gene product whose expression is inhibited by an antisense nucleic acid comprising a nucleotide sequence selected from the group

5   consisting of SEQ ID NOs.: 1-6213, a gene product encoded by a nucleic acid comprising a nucleotide sequence which hybridizes to a nucleic acid selected from the group consisting of SEQ ID NOs.: 1-6213 under stringent conditions, a gene product encoded by a nucleic acid comprising a nucleotide sequence which hybridizes to a nucleic acid selected from the group consisting of SEQ ID NOs.: 1-6213 under moderate conditions, and a gene product

10   whose activity may be complemented by the gene product whose activity is inhibited by a nucleic acid selected from the group consisting of SEQ ID NOs: 1-6213;

    (b) contacting the sensitized cell with a compound; and

    (c) determining the extent to which said compound inhibits the growth of said sensitized cell relative to a cell which does not contain said antisense nucleic acid.

15   296.   The method of Paragraph 295, wherein said determining step comprises determining whether said compound inhibits the growth of said sensitized cell to a greater extent than said compound inhibits the growth of a nonsensitized cell.

    297.   The method of Paragraph 295, wherein said cell is selected from the group consisting of bacterial cells, fungal cells, plant cells, and animal cells.

20   298.   The method of Paragraph 295, wherein said cell is a Gram positive bacterium.

    299.   The method of Paragraph 298, wherein said Gram positive bacterium is selected from the group consisting of *Staphylococcus* species, *Streptococcus* species, *Enterococcus* species, *Mycobacterium* species, *Clostridium* species, and *Bacillus* species.

    300.   The method of Paragraph 299, wherein said Gram positive bacterium is

25   *Staphylococcus aureus*.

    301.   The method of Paragraph 298, wherein said Gram positive bacterium is selected from the group consisting of *Staphylococcus aureus* RN450 and *Staphylococcus aureus* RN4220.

    302.   The method of Paragraph 295, wherein said cell is selected from the group consisting of *Acinetobacter baumannii, Anaplasma marginale, Aspergillus fumigatus, Bacillus*

30   *anthracis, Bacteroides fragilis, Bordetella pertussis, Borrelia burgdorferi, Burkholderia cepacia, Burkholderia fungorum, Burkholderia mallei, Campylobacter jejuni, Candida albicans, Candida glabrata* (also called *Torulopsis glabrata*), *Candida tropicalis, Candida parapsilosis, Candida guilliermondii, Candida krusei, Candida kefyr* (also called *Candida pseudotropicalis*), *Candida dubliniensis, Chlamydia pneumoniae, Chlamydia trachomatis, Clostridium acetobutylicum,*

35   *Clostridium botulinum, Clostridium difficile, Clostridium perfringens, Coccidioides immitis, Corynebacterium diptheriae, Cryptococcus neoformans, Enterobacter cloacae, Enterococcus faecalis, Enterococcus faecium, Escherichia coli, Haemophilus influenzae, Helicobacter pylori, Histoplasma capsulatum, Klebsiella pneumoniae, Legionella pneumophila, Listeria*

monocytogenes, Moraxella catarrhalis, Mycobacterium avium, Mycobacterium bovis, Mycobacterium leprae, Mycobacterium tuberculosis, Mycoplasma genitalium, Mycoplasma pneumoniae, Neisseria gonorrhoeae, Neisseria meningitidis, Nocardia asteroides, Pasteurella haemolytica, Pasteurella multocida, Pneumocystis carinii, Proteus mirabilis, Proteus vulgaris, Pseudomonas aeruginosa, Pseudomonas putida, Pseudomonas syringae, Salmonella bongori, Salmonella cholerasuis, Salmonella enterica, Salmonella paratyphi, Salmonella typhi, Salmonella typhimurium, Shigella boydii, Shigella dysenteriae, Shigella flexneri, Shigella sonnei, Staphylococcus aureus, Staphylococcus epidermidis, Staphylococcus haemolyticus, Streptococcus pneumoniae, Streptococcus mutans, Streptococcus pyogenes, Treponema pallidum, Ureaplasma urealyticum, Vibrio cholerae, Vibrio parahaemolyticus, Vibrio vulnificans, Yersinia enterocolitica, Yersinia pestis and any species falling within the genera of any of the above species.

303. The method of Paragraph 295, wherein said cell is not an *E. coli* cell.

304. The method of Paragraph 295, wherein said gene product is from an organism other than *E. coli*.

305. The method of Paragraph 295, wherein said antisense nucleic acid is transcribed from an inducible promoter.

306. The method of Paragraph 305, further comprising contacting the cell with an agent which induces expression of said antisense nucleic acid from said inducible promoter, wherein said antisense nucleic acid is expressed at a sublethal level.

307. The method of Paragraph 295, wherein inhibition of proliferation is measured by monitoring the optical density of a liquid culture.

308. The method of Paragraph 295, wherein said gene product comprises a polypeptide having at least 25% amino acid identity as determined using FASTA version 3.0t78 with the default parameters to a sequence selected from the group consisting of SEQ ID NOs.: 42398-78581.

309. The method of Paragraph 295, wherein said nucleic acid encoding said gene product comprises a nucleic acid selected from the group consisting of a nucleic acid comprising a nucleic acid having at least 70% nucleotide sequence identity as determined using BLASTN version 2.0 with the default parameters to a nucleotide sequence selected from the group consisting of SEQ ID NOS.: 6214-42397, a nucleic acid comprising a nucleotide sequence which hybridizes to a nucleotide sequence selected from the group consisting of SEQ ID NOS.: 6214-42397 under stringent conditions, and a nucleic acid comprising a nucleotide sequence which hybridizes to a nucleotide sequence selected from the group consisting of SEQ ID NOS.: 6214-42397 under moderate condtions.

310. A compound identified using the method of Paragraph 295.

311. A method for identifying a compound having the ability to inhibit cellular proliferation comprising:

(a) contacting a cell with an agent which reduces the activity or level of a gene product required for proliferation of said cell, wherein said gene product is selected from

the group consisting of a gene product having at least 70% nucleotide sequence identity as determined using BLASTN version 2.0 with the default parameters to a gene product whose expression is inhibited by an antisense nucleic acid comprising a nucleotide sequence selected from the group consisting of SEQ ID NOs.: 1-6213, a gene product encoded by a nucleic acid having at least 70% nucleotide sequence identity as determined using BLASTN version 2.0 with the default parameters to a nucleic acid encoding a gene product whose expression is inhibited by an antisense nucleic acid comprising a nucleotide sequence selected from the group consisting of SEQ ID NOs: 1-6213, a gene product having at least 25% amino acid identity as determined using FASTA version 3.0t78 with the default parameters to a gene product whose expression is inhibited by an antisense nucleic acid comprising a nucleotide sequence selected from the group consisting of SEQ ID NOs.: 1-6213, a gene product encoded by a nucleic acid comprising a nucleotide sequence which hybridizes to a nucleic acid selected from the group consisting of SEQ ID NOs.: 1-6213 under stringent conditions, a gene product encoded by a nucleic acid comprising a nucleotide sequence which hybridizes to a nucleic acid selected from the group consisting of SEQ ID NOs.: 1-6213 under moderate conditions, and a gene product whose activity may be complemented by the gene product whose activity is inhibited by a nucleic acid selected from the group consisting of SEQ ID NOs: 1-6213; ·

(b) contacting said cell with a compound; and

(c) determining the degree to which said compound reduces proliferation of said contacted cell relative to a cell which was not contacted with said agent.

312.   The method of Paragraph 311, wherein said determining step comprises determining whether said compound reduces proliferation of said contacted cell to a greater extent than said compound reduces proliferation of cells which have not been contacted with said agent.

313.   The method of Paragraph 311, wherein said cell is selected from the group consisting of *Acinetobacter baumannii, Anaplasma marginale, Aspergillus fumigatus, Bacillus anthracis, Bacteroides fragilis, Bordetella pertussis, Borrelia burgdorferi, Burkholderia cepacia, Burkholderia fungorum, Burkholderia mallei, Campylobacter jejuni, Candida albicans, Candida glabrata* (also called *Torulopsis glabrata*), *Candida tropicalis, Candida parapsilosis, Candida guilliermondii, Candida krusei, Candida kefyr* (also called *Candida pseudotropicalis*), *Candida dubliniensis, Chlamydia pneumoniae, Chlamydia trachomatis, Clostridium acetobutylicum, Clostridium botulinum, Clostridium difficile, Clostridium perfringens, Coccidioides immitis, Corynebacterium diptheriae, Cryptococcus neoformans, Enterobacter cloacae, Enterococcus faecalis, Enterococcus faecium, Escherichia coli, Haemophilus influenzae, Helicobacter pylori, Histoplasma capsulatum, Klebsiella pneumoniae, Legionella pneumophila, Listeria monocytogenes, Moraxella catarrhalis, Mycobacterium avium, Mycobacterium bovis, Mycobacterium leprae, Mycobacterium tuberculosis, Mycoplasma genitalium, Mycoplasma pneumoniae, Neisseria gonorrhoeae, Neisseria meningitidis, Nocardia asteroides, Pasteurella*

haemolytica, Pasteurella multocida, Pneumocystis carinii, Proteus mirabilis, Proteus vulgaris, Pseudomonas aeruginosa, Pseudomonas putida, Pseudomonas syringae, Salmonella bongori, Salmonella cholerasuis, Salmonella enterica, Salmonella paratyphi, Salmonella typhi, Salmonella typhimurium, Shigella boydii, Shigella dysenteriae, Shigella flexneri, Shigella sonnei, Staphylococcus aureus, Staphylococcus epidermidis, Staphylococcus haemolyticus, Streptococcus pneumoniae, Streptococcus mutans, Streptococcus pyogenes, Treponema pallidum, Ureaplasma urealyticum, Vibrio cholerae, Vibrio parahaemolyticus, Vibrio vulnificans, Yersinia enterocolitica, Yersinia pestis and any species falling within the genera of any of the above species.

314.   The method of Paragraph 311, wherein said cell is not an *E. coli* cell.

315.   The method of Paragraph 311, wherein said gene product is from an organism other than *E. coli*.

316.   The method of Paragraph 311, wherein said agent which reduces the activity or level of a gene product required for proliferation of said cell comprises an antisense nucleic acid to a gene or operon required for proliferation.

317.   The method of Paragraph 311, wherein said agent which reduces the activity or level of a gene product required for proliferation of said cell comprises a compound known to inhibit growth or proliferation of a cell.

318.   The method of Paragraph 311, wherein said cell contains a mutation which reduces the activity or level of said gene product required for proliferation of said cell.

319.   The method of Paragraph 311, wherein said mutation is a temperature sensitive mutation.

320.   The method of Paragraph 311, wherein said gene product comprises a gene product comprises a polypeptide having at least 25% amino acid identity as determined using FASTA version 3.0t78 with the default parameters to an amino acid sequence selected from the group consisting of SEQ ID NOs.: 42398-78581.

321.   A compound identified using the method of Paragraph 311.

322.   A method for identifying the biological pathway in which a proliferation-required gene product or a gene encoding a proliferation-required gene product lies comprising:

        (a) providing a sublethal level of an antisense nucleic acid which inhibits the activity or reduces the level of said gene encoding a proliferation-required gene product or said said proliferation-required gene product in a test cell, wherein said proliferation-required gene product is selected from the group consisting of a gene product having at least 70% nucleotide sequence identity as determined using BLASTN version 2.0 with the default parameters to a gene product whose expression is inhibited by an antisense nucleic acid comprising a nucleotide sequence selected from the group consisting of SEQ ID NOs.: 1-6213, a gene product encoded by a nucleic acid having at least 70% nucleotide sequence identity as determined using BLASTN version 2.0 with the default parameters to a nucleic acid encoding a gene product whose expression is inhibited by an antisense nucleic acid

comprising a nucleotide sequence selected from the group consisting of SEQ ID NOs:1-6213, a gene product having at least 25% amino acid identity as determined using FASTA version 3.0t78 with the default parameters to a gene product whose expression is inhibited by an antisense nucleic acid comprising a nucleotide sequence selected from the group

5   consisting of SEQ ID NOs.: 1-6213, a gene product encoded by a nucleic acid comprising a nucleotide sequence which hybridizes to a nucleic acid selected from the group consisting of SEQ ID NOs.: 1-6213 under stringent conditions, a gene product encoded by a nucleic acid comprising a nucleotide sequence which hybridizes to a nucleic acid selected from the group consisting of SEQ ID NOs.: 1-6213 under moderate conditions, and a gene product

10   whose activity may be complemented by the gene product whose activity is inhibited by a nucleic acid selected from the group consisting of SEQ ID NOs: 1-6213;

(b) contacting said test cell with a compound known to inhibit growth or proliferation of a cell, wherein the biological pathway on which said compound acts is known; and

15   (c) determining the degree to which said compound inhibits proliferation of said test cell relative to a cell which does not contain said antisense nucleic acid.

323.   The method of Paragraph 322, wherein said determining step comprises determining whether said test cell has a substantially greater sensitivity to said compound than a cell which does not express said sublethal level of said antisense nucleic acid.

20   324.   The method of Paragraph 322, wherein said gene product comprises a polypeptide having at least 25% amino acid identity as determined using FASTA version 3.0t78 with the default parameters to an amino acid sequence selected from the group consisting of SEQ ID NOs.: 42398-78581.

325.   The method of Paragraph 322, wherein said test cell is selected from the group

25   consisting of *Acinetobacter baumannii, Anaplasma marginale, Aspergillus fumigatus, Bacillus anthracis, Bacteroides fragilis, Bordetella pertussis, Borrelia burgdorferi, Burkholderia cepacia, Burkholderia fungorum, Burkholderia mallei, Campylobacter jejuni, Candida albicans, Candida glabrata* (also called *Torulopsis glabrata*), *Candida tropicalis, Candida parapsilosis, Candida guilliermondii, Candida krusei, Candida kefyr* (also called *Candida pseudotropicalis*), *Candida*

30   *dubliniensis, Chlamydia pneumoniae, Chlamydia trachomatis, Clostridium acetobutylicum, Clostridium botulinum, Clostridium difficile, Clostridium perfringens, Coccidioides immitis, Corynebacterium diptheriae, Cryptococcus neoformans, Enterobacter cloacae, Enterococcus faecalis, Enterococcus faecium, Escherichia coli, Haemophilus influenzae, Helicobacter pylori, Histoplasma capsulatum, Klebsiella pneumoniae, Legionella pneumophila, Listeria*

35   *monocytogenes, Moraxella catarrhalis, Mycobacterium avium, Mycobacterium bovis, Mycobacterium leprae, Mycobacterium tuberculosis, Mycoplasma genitalium, Mycoplasma pneumoniae, Neisseria gonorrhoeae, Neisseria meningitidis, Nocardia asteroides, Pasteurella haemolytica, Pasteurella multocida, Pneumocystis carinii, Proteus mirabilis, Proteus vulgaris,*

Pseudomonas aeruginosa, Pseudomonas putida, Pseudomonas syringae, Salmonella bongori, Salmonella cholerasuis, Salmonella enterica, Salmonella paratyphi, Salmonella typhi, Salmonella typhimurium, Shigella boydii, Shigella dysenteriae, Shigella flexneri, Shigella sonnei, Staphylococcus aureus, Staphylococcus epidermidis, Staphylococcus haemolyticus, Streptococcus pneumoniae, Streptococcus mutans, Streptococcus pyogenes, Treponema pallidum, Ureaplasma urealyticum, Vibrio cholerae, Vibrio parahaemolyticus, Vibrio vulnificans, Yersinia enterocolitica, Yersinia pestis and any species falling within the genera of any of the above species.

326. The method of Paragraph 322, wherein said test cell is not an *E. coli* cell.

327. The method of Paragraph 322, wherein said gene product is from an organism other than *E. coli*.

328. A method for determining the biological pathway on which a test compound acts comprising:

(a) providing a sublethal level of an antisense nucleic acid complementary to a proliferation-required nucleic acid in a cell, thereby producing a sensitized cell, wherein said antisense nucleic acid is selected from the group consisting of a nucleic acid having at least 70% nucleotide sequence identity as determined using BLASTN version 2.0 with the default parameters to a nucleotide sequence selected from the group consisting of SEQ ID NOs:1-6213 or a proliferation-inhibiting portion thereof,a nucleic acid comprising a nucleotide sequence which hybridizes to a nucleic acid selected from the group consisting of SEQ ID NOs.: 1-6213 under stringent conditions, and a nucleic acid comprising a nucleotide sequence which hybridizes to a nucleic acid selected from the group consisting of SEQ ID NOs.: 1-6213 under moderate conditions and wherein the biological pathway in which said proliferation-required nucleic acid or a protein encoded by said proliferation-required polypeptide lies is known,

(b) contacting said cell with said test compound; and

(c) determining the degree to which said compound inhibits proliferation of said sensitized cell relative to a cell which does not contain said antisense nucleic acid.

329. The method of Paragraph 328, wherein said determining step comprises determining whether said sensitized cell has a substantially greater sensitivity to said test compound than a cell which does not express said sublethal level of said antisense nucleic acid.

330. The method of Paragraph 328, further comprising:

(d) providing a sublethal level of a second antisense nucleic acid complementary to a second proliferation-required nucleic acid in a second cell, wherein said second proliferation-required nucleic acid is in a different biological pathway than said proliferation-required nucleic acid in step (a); and

(e) determining whether said second cell does not have a substantially greater sensitivity to said test compound than a cell which does not express said sublethal level of said second antisense nucleic acid, wherein said test compound is specific for the biological

pathway against which the antisense nucleic acid of step (a) acts if said sensitized cell has substantially greater sensitivity to said test compound than said second cell.

331.   The method of Paragraph 328, wherein said sensitized cell is selected from the group consisting of *Acinetobacter baumannii, Anaplasma marginale, Aspergillus fumigatus, Bacillus anthracis, Bacteroides fragilis, Bordetella pertussis, Borrelia burgdorferi, Burkholderia cepacia. Burkholderia fungorum. Burkholderia mallei, Campylobacter jejuni, Candida albicans, Candida glabrata* (also called *Torulopsis glabrata*), *Candida tropicalis, Candida parapsilosis, Candida guilliermondii, Candida krusei, Candida kefyr* (also called *Candida pseudotropicalis*), *Candida dubliniensis, Chlamydia pneumoniae, Chlamydia trachomatis, Clostridium acetobutylicum, Clostridium botulinum, Clostridium difficile, Clostridium perfringens, Coccidioides immitis, Corynebacterium diptheriae, Cryptococcus neoformans, Enterobacter cloacae, Enterococcus faecalis, Enterococcus faecium, Escherichia coli, Haemophilus influenzae, Helicobacter pylori, Histoplasma capsulatum, Klebsiella pneumoniae, Legionella pneumophila, Listeria monocytogenes, Moraxella catarrhalis, Mycobacterium avium, Mycobacterium bovis, Mycobacterium leprae, Mycobacterium tuberculosis, Mycoplasma genitalium, Mycoplasma pneumoniae, Neisseria gonorrhoeae, Neisseria meningitidis, Nocardia asteroides, Pasteurella haemolytica, Pasteurella multocida, Pneumocystis carinii. Proteus mirabilis, Proteus vulgaris, Pseudomonas aeruginosa, Pseudomonas putida, Pseudomonas syringae, Salmonella bongori, Salmonella cholerasuis, Salmonella enterica, Salmonella paratyphi, Salmonella typhi, Salmonella typhimurium, Shigella boydii, Shigella dysenteriae, Shigella flexneri, Shigella sonnei, Staphylococcus aureus, Staphylococcus epidermidis, Staphylococcus haemolyticus, Streptococcus pneumoniae, Streptococcus mutans, Streptococcus pyogenes, Treponema pallidum, Ureaplasma urealyticum, Vibrio cholerae, Vibrio parahaemolyticus, Vibrio vulnificans, Yersinia enterocolitica, Yersinia pestis* and any species failing within the genera of any of the above species.

332.   The method of Paragraph 328, wherein said sensitized cell is not an *E. coli* cell.

333.   The method of Paragraph 328, wherein said proliferation-required nucleic acid is from an organism other than *E. coli*.

334.   A compound which inhibits proliferation by interacting with a gene encoding a gene product required for proliferation or with a gene product required for proliferation, wherein said gene product is selected from the group consisting of a gene product having at least 70% nucleotide sequence identity as determined using BLASTN version 2.0 with the default parameters to a gene product whose expression is inhibited by an antisense nucleic acid comprising a nucleotide sequence selected from the group consisting of SEQ ID NOs.: 1-6213, a gene product encoded by a nucleic acid having at least 70% nucleotide sequence identity as determined using BLASTN version 2.0 with the default parameters to a nucleic acid encoding a gene product whose expression is inhibited by an antisense nucleic acid comprising a nucleotide sequence selected from the group consisting of SEQ ID NOs:1-6213, a gene product having at least 25% amino acid identity as determined using FASTA version 3.0t78 with the default parameters to a gene product

whose expression is inhibited by an antisense nucleic acid comprising a nucleotide sequence selected from the group consisting of SEQ ID NOs.: 1-6213, a gene product encoded by a nucleic acid comprising a nucleotide sequence which hybridizes to a nucleic acid selected from the group consisting of SEQ ID NOs.: 1-6213 under stringent conditions, a gene product encoded by a nucleic

5   acid comprising a nucleotide sequence which hybridizes to a nucleic acid selected from the group consisting of SEQ ID NOs.: 1-6213 under moderate conditions, and a gene product whose activity may be complemented by the gene product whose activity is inhibited by a nucleic acid selected from the group consisting of SEQ ID NOs: 1-6213.

335.   The compound of Paragraph 334, wherein said gene product comprises a

10   polypeptide having at least 25% amino acid identity as determined using FASTA version 3.0t78 with the default parameters to a sequence selected from the group consisting of SEQ ID NOs.: 42398-78581.

336.   The compound of Paragraph 334, wherein said gene comprises a nucleic acid selected from the group consisting of a nucleic acid comprising a nucleic acid having at least 70%

15   nucleotide sequence identity as determined using BLASTN version 2.0 with the default parameters to a nucleotide sequence selected from the group consisting of SEQ ID NOS.: 6214-42397, a nucleic acid comprising a nucleotide sequence which hybridizes to a nucleotide sequence selected from the group consisting of SEQ ID NOS.: 6214-42397 under stringent conditions, and a nucleic acid comprising a nucleotide sequence which hybridizes to a nucleotide sequence selected from the

20   group consisting of SEQ ID NOS.: 6214-42397 under moderate condtions.

337.   A method for manufacturing an antibiotic comprising the steps of:

screening one or more candidate compounds to identify a compound that reduces the activity or level of a gene product required for proliferation wherein said gene product is selected from the group consisting of a gene product having at least 70% nucleotide sequence identity as

25   determined using BLASTN version 2.0 with the default parameters to a gene product whose expression is inhibited by an antisense nucleic acid comprising a nucleotide sequence selected from the group consisting of SEQ ID NOs.: 1-6213, a gene product encoded by a nucleic acid having at least 70% nucleotide sequence identity as determined using BLASTN version 2.0 with the default parameters to a nucleic acid encoding a gene product whose expression is inhibited by an antisense

30   nucleic acid comprising a nucleotide sequence selected from the group consisting of SEQ ID NOs:1-6213, a gene product having at least 25% amino acid identity as determined using FASTA version 3.0t78 with the default parameters to a gene product whose expression is inhibited by an antisense nucleic acid comprising a nucleotide sequence selected from the group consisting of SEQ ID NOs.: 1-6213, a gene product encoded by a nucleic acid comprising a nucleotide sequence .

35   which hybridizes to a nucleic acid selected from the group consisting of SEQ ID NOs.: 1-6213 under stringent conditions, a gene product encoded by a nucleic acid comprising a nucleotide sequence which hybridizes to a nucleic acid selected from the group consisting of SEQ ID NOs.: 1-6213 under moderate conditions, and a gene product whose activity may be complemented by the

gene product whose activity is inhibited by a nucleic acid selected from the group consisting of SEQ ID NOs: 1-6213 ; and

> manufacturing the compound so identified.

338. The method of Paragraph 337, wherein said screening step comprises performing any one of the methods of Paragraphs 205, 211, 222, 275, 290, 295, 311.

339. The method of Paragraph 337, wherein said gene product comprises a polypeptide having at least 25% amino acid identity as determined using FASTA version 3.0t78 with the default parameters to an amino acid sequence selected from the group consisting of SEQ ID NOs.: 42398-78581.

340. A method for inhibiting proliferation of a cell in a subject comprising administering an effective amount of a compound that reduces the activity or level of a gene product required for proliferation of said cell, wherein said gene product is selected from the group consisting of a gene product having at least 70% nucleotide sequence identity as determined using BLASTN version 2.0 with the default parameters to a gene product whose expression is inhibited by an antisense nucleic acid comprising a nucleotide sequence selected from the group consisting of SEQ ID NOs.: 1-6213, a gene product encoded by a nucleic acid having at least 70% nucleotide sequence identity as determined using BLASTN version 2.0 with the default parameters to a nucleic acid encoding a gene product whose expression is inhibited by an antisense nucleic acid comprising a nucleotide sequence selected from the group consisting of SEQ ID NOs: 1-6213, a gene product having at least 25% amino acid identity as determined using FASTA version 3.0t78 with the default parameters to a gene product whose expression is inhibited by an antisense nucleic acid comprising a nucleotide sequence selected from the group consisting of SEQ ID NOs.: 1-6213, a gene product encoded by a nucleic acid comprising a nucleotide sequence which hybridizes to a nucleic acid selected from the group consisting of SEQ ID NOs.: 1-6213 under stringent conditions, a gene product encoded by a nucleic acid comprising a nucleotide sequence which hybridizes to a nucleic acid selected from the group consisting of SEQ ID NOs.: 1-6213 under moderate conditions, and a gene product whose activity may be complemented by the gene product whose activity is inhibited by a nucleic acid selected from the group consisting of SEQ ID NOs: 1-6213.

341. The method of Paragraph 340 wherein said subject is selected from the group consisting of vertebrates, mammals, avians, and human beings.

342. The method of Paragraph 340, wherein said gene product comprises a polypeptide having at least 25% amino acid identity as determined using FASTA version 3.0t78 with the default parameters to an amino acid sequence selected from the group consisting of SEQ ID NOs.: 42398-78581.

343. The method of Paragraph 340, wherein said cell is selected from the group consisting of *Acinetobacter baumannii, Anaplasma marginale, Aspergillus fumigatus, Bacillus anthracis, Bacteroides fragilis, Bordetella pertussis, Borrelia burgdorferi, Burkholderia cepacia, Burkholderia fungorum, Burkholderia mallei, Campylobacter jejuni, Candida albicans, Candida*

glabrata (also called *Torulopsis glabrata*), *Candida tropicalis, Candida parapsilosis, Candida guilliermondii, Candida krusei, Candida kefyr* (also called *Candida pseudotropicalis*), *Candida dubliniensis, Chlamydia pneumoniae, Chlamydia trachomatis, Clostridium acetobutylicum, Clostridium botulinum, Clostridium difficile, Clostridium perfringens, Coccidioides immitis,*
5 *Corynebacterium diptheriae, Cryptococcus neoformans, Enterobacter cloacae, Enterococcus faecalis, Enterococcus faecium, Escherichia coli, Haemophilus influenzae, Helicobacter pylori, Histoplasma capsulatum, Klebsiella pneumoniae, Legionella pneumophila, Listeria monocytogenes, Moraxella catarrhalis, Mycobacterium avium, Mycobacterium bovis, Mycobacterium leprae, Mycobacterium tuberculosis, Mycoplasma genitalium, Mycoplasma*
10 *pneumoniae, Neisseria gonorrhoeae, Neisseria meningitidis, Nocardia asteroides, Pasteurella haemolytica, Pasteurella multocida, Pneumocystis carinii, Proteus mirabilis, Proteus vulgaris, Pseudomonas aeruginosa, Pseudomonas putida, Pseudomonas syringae, Salmonella bongori, Salmonella cholerasuis, Salmonella enterica, Salmonella paratyphi, Salmonella typhi, Salmonella typhimurium, Shigella boydii, Shigella dysenteriae, Shigella flexneri, Shigella sonnei,*
15 *Staphylococcus aureus, Staphylococcus epidermidis, Staphylococcus haemolyticus, Streptococcus pneumoniae, Streptococcus mutans, Streptococcus pyogenes, Treponema pallidum, Ureaplasma urealyticum, Vibrio cholerae, Vibrio parahaemolyticus, Vibrio vulnificans, Yersinia enterocolitica, Yersinia pestis* and any species falling within the genera of any of the above species.

344.   The method of Paragraph 340, wherein said cell is not *E. coli.*

20   345.   The method of Paragraph 340, wherein said gene product is from an organism other than *E. coli.*

346.   A method for identifying the gene product on which a compound which inhibits proliferation of an organism acts comprising:

obtaining a culture comprising a plurality of strains wherein each strain in said
25   culture overexpresses a different gene product which is essential for proliferation of said organism, wherein said culture comprises a strain in which a gene product whose activity or level is inhibited by a nucleic acid comprising a nucleotide sequence selected from the group consisting of SEQ ID NOs.: 1-6213 is overexpressed;

contacting said culture with a sufficient concentration of said compound to inhibit
30   the proliferation of strains of said organism which do not overexpress said gene product on which said compound acts, such that strains which overexpress said gene product on which said compound acts proliferate more rapidly than strains which do not overexpress said gene product on which said compound acts; and

identifying the gene product which is overexpressed in a strain which proliferated
35   more rapidly in said culture.

347.   A method for identifying the gene product on which a compound which inhibits proliferation of an organism acts comprising:

obtaining a culture comprising a plurality of strains wherein each strain in said culture overexpresses a different gene product which is essential for proliferation of said organism, wherein said culture comprises a strain in which a gene product encoded by a nucleic acid comprising a nucleotide sequence selected from the group consisting of SEQ ID NOs.: 6214-42397 is overexpressed;

contacting said culture with a sufficient concentration of said compound to inhibit the proliferation of strains of said organism which do not overexpress said gene product on which said compound acts, such that strains which overexpress said gene product on which said compound acts proliferate more rapidly than strains which do not overexpress said gene product on which said compound acts; and

identifying the gene product which is overexpressed in a strain which proliferated more rapidly in said culture.

348.   A method for identifying the gene product on which a compound which inhibits proliferation of an organism acts comprising:

obtaining a culture comprising a plurality of strains wherein each strain in said culture overexpresses a different gene product which is essential for proliferation of said organism, wherein said culture comprises a strain in which a gene product comprising an amino acid sequence selected from the group consisting of SEQ ID NOs.: 42938-78581 is overexpressed;

contacting said culture with a sufficient concentration of said compound to inhibit the proliferation of strains of said organism which do not overexpress said gene product on which said compound acts, such that strains which overexpress said gene product on which said compound acts proliferate more rapidly than strains which do not overexpress said gene product on which said compound acts; and

identifying the gene product which is overexpressed in a strain which proliferated more rapidly in said culture.

349.   A method for identifying the gene product on which a compound which inhibits proliferation of an organism acts comprising:

obtaining a culture comprising a plurality of strains wherein each strain in said culture overexpresses a different gene product which is essential for proliferation of said organism, wherein said culture comprises a strain in which a gene product selected from the group consisting of a gene product having at least 70% nucleotide sequence identity as determined using BLASTN version 2.0 with the default parameters to a gene product whose expression is inhibited by an antisense nucleic acid comprising a nucleotide sequence selected from the group consisting of SEQ ID NOs.: 1-6213, a gene product encoded by a nucleic acid having at least 70% nucleotide sequence identity as determined using BLASTN version 2.0 with the default parameters to a nucleic acid encoding a gene product whose expression is inhibited by an antisense nucleic acid comprising a nucleotide

sequence selected from the group consisting of SEQ ID NOs: 1-6213, a gene product having at least 25% amino acid identity as determined using FASTA version 3.0t78 with the default parameters to a gene product whose expression is inhibited by an antisense nucleic acid comprising a nucleotide sequence selected from the group consisting of SEQ ID NOs.: 1-6213, a gene product encoded by a nucleic acid which hybridizes to a nucleic acid comprising a nucleotide sequence selected from the group consisting of SEQ ID NOs.: 1-6213 under stringent conditions, a gene product encoded by a nucleic acid which hybridizes to a nucleic acid comprising a nucleotide sequence selected from the group consisting of SEQ ID NOs.: 1-6213 under moderate conditions, and a gene product whose activity may be complemented by the gene product whose activity is inhibited by a nucleic acid comprising a nucleotide sequence selected from the group consisting of SEQ ID NOs: 1-6213 is overexpressed;

contacting said culture with a sufficient concentration of said compound to inhibit the proliferation of strains of said organism which do not overexpress said gene product on which said compound acts, such that strains which overexpress said gene product on which said compound acts proliferate more rapidly than strains which do not overexpress said gene product on which said compound acts; and

identifying the gene product which is overexpressed in a strain which proliferated more rapidly in said culture.

350.   A method for identifying the gene product on which a compound which inhibits proliferation of an organism acts comprising:

obtaining a culture comprising a plurality of strains wherein each strain in said culture overexpresses a different gene product which is essential for proliferation of said organism, wherein said culture comprises a strain in which a gene product encoded by a nucleic acid comprising a nucleotide sequence selected from the group consisting of a nucleic acid comprising a nucleic acid having at least 70% nucleotide sequence identity as determined using BLASTN version 2.0 with the default parameters to a nucleotide sequence selected from the group consisting of SEQ ID NOS.: 6214-42397, a nucleic acid comprising a nucleotide sequence which hybridizes to a sequence selected from the group consisting of SEQ ID NOS.: 6214-42397 under stringent conditions, and a nucleic acid comprising a nucleotide sequence which hybridizes to a nucleotide sequence selected from the group consisting of SEQ ID NOS.: 6214-42397 under moderate conditions is overexpressed;

contacting said culture with a sufficient concentration of said compound to inhibit the proliferation of strains of said organism which do not overexpress said gene product on which said compound acts, such that strains which overexpress said gene product on which said compound acts proliferate more rapidly than strains which do not overexpress said gene product on which said compound acts; and

identifying the gene product which is overexpressed in a strain which proliferated more rapidly in said culture.

351.   A method for identifying the gene product on which a compound which inhibits proliferation of an organism acts comprising:

5   obtaining a culture comprising a plurality of strains wherein each strain in said culture overexpresses a different gene product which is essential for proliferation of said organism, wherein said culture comprises a strain in which a gene product comprises a polypeptide selected from the group consisting of a polypeptide having at least 25% amino acid identity as determined using FASTA version 3.0t78 to a polypeptide selected from the

10   group consisting of SEQ ID NOs.: 42938-78581 and a polypeptide whose activity may be complemented by a polypeptide selected from the group consisting of SEQ ID NOs: 42938-78581 is overexpressed;

contacting said culture with a sufficient concentration of said compound to inhibit the proliferation of strains of said organism which do not overexpress said gene product on

15   which said compound acts, such that strains which overexpress said gene product on which said compound acts proliferate more rapidly than strains which do not overexpress said gene product on which said compound acts; and

identifying the gene product which is overexpressed in a strain which proliferated more rapidly in said culture.

20   352.   The method of Paragraph 346, 347, 348, 349, 350 or 351, wherein said culture includes at least one strain which does not overexpresses a gene product which is essential for proliferation of said organism.

353.   The method of Paragraph 346, 347, 348, 349, 350 or 351, wherein said strains which overexpress said gene products comprise a nucleic acid encoding said gene product which is

25   essential for proliferation of said organism operably linked to a regulatable promoter.

354.   The method of Paragraph 346, 347, 348, 349, 350 or 351, wherein said strains which overexpress said gene products a nucleic acid encoding said gene product which is essential for proliferation of said organism operably linked to a constitutive promoter.

355.   The method of Paragraph 346, 347, 348, 349, 350 or 351, wherein said

30   identification step comprises determining the nucleotide sequence of a nucleic acid encoding said gene product in said cell which proliferated more rapidly in said culture.

356.   The method of Paragraph 346, 347, 348, 349, 350 or 351, wherein said identification step comprises performing an amplification reaction to identify the nucleic acid encoding said gene product in said cell which proliferated more rapidly in said cell culture.

35   357.   The method of Paragraph 356, wherein the products of said amplification reaction are labeled with a detectable dye.

358.   The method of Paragraph 346, 347, 348, 349, 350 or 351, wherein said identification step comprises performing a hybridization procedure.

359.   The method of Paragraph 346, 347, 348, 349, 350 or 351, wherein said identification step comprises contacting a nucleic acid array with a nucleic acid encoding said gene product in said cell which proliferated more rapidly in said cell culture.

360.   The method of Paragraph 346, 347, 348, 349, 350 or 351, wherein said organism is selected from the group consisting of bacteria, fungi, and protozoa.

361.   The method of Paragraph 346, 347, 348, 349, 350 or 351, wherein said culture is a culture of an organism selected from the group consisting of *Acinetobacter baumannii, Anaplasma marginale, Aspergillus fumigatus, Bacillus anthracis, Bacteroides fragilis, Bordetella pertussis, Borrelia burgdorferi, Burkholderia cepacia, Burkholderia fungorum, Burkholderia mallei, Campylobacter jejuni, Candida albicans, Candida glabrata* (also called *Torulopsis glabrata*), *Candida tropicalis, Candida parapsilosis, Candida guilliermondii, Candida krusei, Candida kefyr* (also called *Candida pseudotropicalis*), *Candida dubliniensis, Chlamydia pneumoniae, Chlamydia trachomatis, Clostridium acetobutylicum, Clostridium botulinum, Clostridium difficile, Clostridium perfringens, Coccidioides immitis, Corynebacterium diptheriae, Cryptococcus neoformans, Enterobacter cloacae, Enterococcus faecalis, Enterococcus faecium, Escherichia coli, Haemophilus influenzae, Helicobacter pylori, Histoplasma capsulatum, Klebsiella pneumoniae, Legionella pneumophila, Listeria monocytogenes, Moraxella catarrhalis, Mycobacterium avium, Mycobacterium bovis, Mycobacterium leprae, Mycobacterium tuberculosis, Mycoplasma genitalium, Mycoplasma pneumoniae, Neisseria gonorrhoeae, Neisseria meningitidis, Nocardia asteroides, Pasteurella haemolytica, Pasteurella multocida, Pneumocystis carinii, Proteus mirabilis, Proteus vulgaris, Pseudomonas aeruginosa, Pseudomonas putida, Pseudomonas syringae, Salmonella bongori, Salmonella cholerasuis, Salmonella enterica, Salmonella paratyphi, Salmonella typhi, Salmonella typhimurium, Shigella boydii, Shigella dysenteriae, Shigella flexneri, Shigella sonnei, Staphylococcus aureus, Staphylococcus epidermidis, Staphylococcus haemolyticus, Streptococcus pneumoniae, Streptococcus mutans, Streptococcus pyogenes, Treponema pallidum, Ureaplasma urealyticum, Vibrio cholerae, Vibrio parahaemolyticus, Vibrio vulnificans, Yersinia enterocolitica, Yersinia pestis* and any species falling within the genera of any of the above species.

362.   The method of Paragraph 346, 347, 348, 349, 350 or 351, wherein said compound is obtained from a library of natural compounds.

363.   The method of Paragraph 346, 347, 348, 349, 350 or 351, wherein said compound is obtained from a library of synthetic compounds.

364.   The method of Paragraph 346, 347, 348, 349, 350 or 351, wherein said compound is present in a crude or partially purified state.

365.   The method of Paragraph 346, 347, 348, 349, 350 or 351, further comprising determining whether said gene product in said strain which proliferated more rapidly in said culture has a counterpart in at least one other organism.

366.   A method for identifying the gene product on which a compound which inhibits proliferation of an organism acts comprising:

obtaining an array of strains on a solid growth medium wherein each strain overexpresses a different gene product which is essential for proliferation of said organism, wherein said culture comprises a strain in which a gene product whose activity or level is inhibited by a nucleic acid comprising a nucleotide sequence selected from the group

5   consisting of SEQ ID NOs.: 1-6213 is overexpressed;

contacting said array of strains with a sufficient concentration of said compound to inhibit the proliferation of strains of said organism which do not overexpress said gene product on which said compound acts, such that strains which overexpress said gene product on which said compound acts proliferate more rapidly than strains which do not

10   overexpress said gene product on which said compound acts; and

identifying the gene product which is overexpressed in a strain which proliferated more rapidly on said solid medium.

367.   A method for identifying the gene product on which a compound which inhibits proliferation of an organism acts comprising:

15   obtaining an array of strains on a solid growth medium wherein each strain overexpresses a different gene product which is essential for proliferation of said organism, wherein said culture comprises a strain in which a gene product encoded by a nucleic acid comprising a nucleotide sequence selected from the group consisting of SEQ ID NOs.: 6214-42397 is overexpressed;

20   contacting said array of strains with a sufficient concentration of said compound to inhibit the proliferation of strains of said organism which do not overexpress said gene product on which said compound acts, such that strains which overexpress said gene product on which said compound acts proliferate more rapidly than strains which do not overexpress said gene product on which said compound acts; and

25   identifying the gene product which is overexpressed in a strain which proliferated more rapidly on said solid medium.

368.   A method for identifying the gene product on which a compound which inhibits proliferation of an organism acts comprising:

obtaining an array of strains on a solid growth medium wherein each strain

30   overexpresses a different gene product which is essential for proliferation of said organism, wherein said culture comprises a strain in which a gene product comprising an amino acid sequence selected from the group consisting of SEQ ID NOs.: 42938-78581 is overexpressed;

contacting said array of strains with a sufficient concentration of said compound to

35   inhibit the proliferation of strains of said organism which do not overexpress said gene product on which said compound acts, such that strains which overexpress said gene product on which said compound acts proliferate more rapidly than strains which do not overexpress said gene product on which said compound acts; and

identifying the gene product which is overexpressed in a strain which proliferated more rapidly on said solid medium.

369.   A method for identifying the gene product on which a compound which inhibits proliferation of an organism acts comprising:

5   obtaining an array of strains on a solid growth medium wherein each strain overexpresses a different gene product which is essential for proliferation of said organism, wherein said culture comprises a strain in which a gene product selected from the group consisting of a gene product having at least 70% nucleotide sequence identity as determined using BLASTN version 2.0 with the default parameters to a gene product whose expression

10   is inhibited by an antisense nucleic acid comprising a nucleotide sequence selected from the group consisting of SEQ ID NOs.: 1-6213, a gene product encoded by a nucleic acid having at least 70% nucleotide sequence identity as determined using BLASTN version 2.0 with the default parameters to a nucleic acid encoding a gene product whose expression is inhibited by an antisense nucleic acid comprising a nucleotide sequence selected from the

15   group consisting of SEQ ID NOs: 1-6213, a gene product having at least 25% amino acid identity as determined using FASTA version 3.0t78 with the default parameters to a gene product whose expression is inhibited by an antisense nucleic acid comprising a nucleotide sequence selected from the group consisting of SEQ ID NOs.: 1-6213, a gene product encoded by a nucleic acid which hybridizes to a nucleic acid comprising a nucleotide

20   sequence selected from the group consisting of SEQ ID NOs.: 1-6213 under stringent conditions, a gene product encoded by a nucleic acid which hybridizes to a nucleic acid comprising a nucleotide sequence selected from the group consisting of SEQ ID NOs.: 1-6213 under moderate conditions, and a gene product whose activity may be complemented by the gene product whose activity is inhibited by a nucleic acid comprising a nucleotide

25   sequence selected from the group consisting of SEQ ID NOs: 1-6213 is overexpressed;

contacting said array of strains with a sufficient concentration of said compound to inhibit the proliferation of strains of said organism which do not overexpress said gene product on which said compound acts, such that strains which overexpress said gene product on which said compound acts proliferate more rapidly than strains which do not

30   overexpress said gene product on which said compound acts; and

identifying the gene product which is overexpressed in a strain which proliferated more rapidly on said solid medium.

370.   A method for identifying the gene product on which a compound which inhibits proliferation of an organism acts comprising:

35   obtaining an array of strains on a solid growth medium wherein each strain overexpresses a different gene product which is essential for proliferation of said organism, wherein said culture comprises a strain in which a gene product encoded by a nucleic acid comprising a nucleotide sequence selected from the group consisting of a nucleic acid

comprising a nucleic acid having at least 70% nucleotide sequence identity as determined using BLASTN version 2.0 with the default parameters to a nucleotide sequence selected from the group consisting of SEQ ID NOS.: 6214-42397, a nucleic acid comprising a nucleotide sequence which hybridizes to a sequence selected from the group consisting of

5   SEQ ID NOS.: 6214-42397 under stringent conditions, and a nucleic acid comprising a nucleotide sequence which hybridizes to a nucleotide sequence selected from the group consisting of SEQ ID NOS.: 6214-42397 under moderate conditions is overexpressed;

contacting said array of strains with a sufficient concentration of said compound to inhibit the proliferation of strains of said organism which do not overexpress said gene

10   product on which said compound acts, such that strains which overexpress said gene product on which said compound acts proliferate more rapidly than strains which do not overexpress said gene product on which said compound acts; and

identifying the gene product which is overexpressed in a strain which proliferated more rapidly on said solid medium.

15   371.   A method for identifying the gene product on which a compound which inhibits proliferation of an organism acts comprising:

obtaining an array of strains on a solid growth medium wherein each strain overexpresses a different gene product which is essential for proliferation of said organism, wherein said culture comprises a strain in which a gene product comprises a polypeptide

20   selected from the group consisting of a polypeptide having at least 25% amino acid identity as determined using FASTA version 3.0t78 to a polypeptide selected from the group consisting of SEQ ID NOs.: 42938-78581 and a polypeptide whose activity may be complemented by a polypeptide selected from the group consisting of SEQ ID NOs: 42938-78581 is overexpressed;

25   contacting said array of strains with a sufficient concentration of said compound to inhibit the proliferation of strains of said organism which do not overexpress said gene product on which said compound acts, such that strains which overexpress said gene product on which said compound acts proliferate more rapidly than strains which do not overexpress said gene product on which said compound acts; and

30   identifying the gene product which is overexpressed in a strain which proliferated more rapidly on said solid medium.

372.   The method of Paragraph 366, 367, 368, 369, 370 or 371, wherein at least one strain in said array does not overexpresses a gene product which is essential for proliferation of said organism.

35   373.   A method for identifying the gene product on which a compound which inhibits proliferation of an organism acts comprising:

obtaining a plurality of cultures, wherein each culture comprises a plurality of strains wherein each strain overexpresses a different gene product which is essential for

proliferation of said organism, wherein said culture comprises a strain in which a gene product whose activity or level is inhibited by a nucleic acid comprising a nucleotide sequence selected from the group consisting of SEQ ID NOs.: 1-6213 is overexpressed;

contacting each of said cultures with a different concentration of said compound;

5   and

identifying the gene product which is overexpressed in a strain whose proliferation is inhibited by said compound.

374.   A method for identifying the gene product on which a compound which inhibits proliferation of an organism acts comprising:

10   obtaining a plurality of cultures, wherein each culture comprises a plurality of strains wherein each strain overexpresses a different gene product which is essential for proliferation of said organism, wherein said culture comprises a strain in which a gene product encoded by a nucleic acid comprising a nucleotide sequence selected from the group consisting of SEQ ID NOs.: 6214-42397 is overexpressed;

15   contacting each of said cultures with a different concentration of said compound; and

identifying the gene product which is overexpressed in a strain whose proliferation is inhibited by said compound.

375.   A method for identifying the gene product on which a compound which inhibits

20   proliferation of an organism acts comprising:

obtaining a plurality of cultures, wherein each culture comprises a plurality of strains wherein each strain overexpresses a different gene product which is essential for proliferation of said organism, wherein said culture comprises a strain in which a gene product comprising an amino acid sequence selected from the group consisting of SEQ ID

25   NOs.: 42938-78581 is overexpressed;

contacting each of said cultures with a different concentration of said compound; and

identifying the gene product which is overexpressed in a strain whose proliferation is inhibited by said compound.

30   376.   A method for identifying the gene product on which a compound which inhibits proliferation of an organism acts comprising:

obtaining a plurality of cultures, wherein each culture comprises a plurality of strains wherein each strain overexpresses a different gene product which is essential for proliferation of said organism, wherein said culture comprises a strain in which a gene

35   product selected from the group consisting of a gene product having at least 70% nucleotide sequence identity as determined using BLASTN version 2.0 with the default parameters to a gene product whose expression is inhibited by an antisense nucleic acid comprising a nucleotide sequence selected from the group consisting of SEQ ID NOs.: 1-6213, a gene

product encoded by a nucleic acid having at least 70% nucleotide sequence identity as determined using BLASTN version 2.0 with the default parameters to a nucleic acid encoding a gene product whose expression is inhibited by an antisense nucleic acid comprising a nucleotide sequence selected from the group consisting of SEQ ID NOs: 1-6213, a gene product having at least 25% amino acid identity as determined using FASTA version 3.0t78 with the default parameters to a gene product whose expression is inhibited by an antisense nucleic acid comprising a nucleotide sequence selected from the group consisting of SEQ ID NOs.: 1-6213, a gene product encoded by a nucleic acid which hybridizes to a nucleic acid comprising a nucleotide sequence selected from the group consisting of SEQ ID NOs.: 1-6213 under stringent conditions, a gene product encoded by a nucleic acid which hybridizes to a nucleic acid comprising a nucleotide sequence selected from the group consisting of SEQ ID NOs.: 1-6213 under moderate conditions, and a gene product whose activity may be complemented by the gene product whose activity is inhibited by a nucleic acid comprising a nucleotide sequence selected from the group consisting of SEQ ID NOs: 1-6213 is overexpressed;

contacting each of said cultures with a different concentration of said compound; and

identifying the gene product which is overexpressed in a strain whose proliferation is inhibited by said compound.

377.   A method for identifying the gene product on which a compound which inhibits proliferation of an organism acts comprising:

obtaining a plurality of cultures, wherein each culture comprises a plurality of strains wherein each strain overexpresses a different gene product which is essential for proliferation of said organism, wherein said culture comprises a strain in which a gene product encoded by a nucleic acid comprising a nucleotide sequence selected from the group consisting of a nucleic acid comprising a nucleic acid having at least 70% nucleotide sequence identity as determined using BLASTN version 2.0 with the default parameters to a nucleotide sequence selected from the group consisting of SEQ ID NOS.: 6214-42397, a nucleic acid comprising a nucleotide sequence which hybridizes to a sequence selected from the group consisting of SEQ ID NOS.: 6214-42397 under stringent conditions, and a nucleic acid comprising a nucleotide sequence which hybridizes to a nucleotide sequence selected from the group consisting of SEQ ID NOS.: 6214-42397 under moderate conditions is overexpressed;

contacting each of said cultures with a different concentration of said compound; and

identifying the gene product which is overexpressed in a strain whose proliferation is inhibited by said compound.

378.   A method for identifying the gene product on which a compound which inhibits proliferation of an organism acts comprising:

obtaining a plurality of cultures, wherein each culture comprises a plurality of strains wherein each strain overexpresses a different gene product which is essential for proliferation of said organism, wherein said culture comprises a strain in which a gene product comprises a polypeptide selected from the group consisting of a polypeptide having at least 25% amino acid identity as determined using FASTA version 3.0t78 to a polypeptide selected from the group consisting of SEQ ID NOs.: 42938-78581 and a polypeptide whose activity may be complemented by a polypeptide selected from the group consisting of SEQ ID NOs: 42938-78581 is overexpressed;

contacting each of said cultures with a different concentration of said compound; and

identifying the gene product which is overexpressed in a strain whose proliferation is inhibited by said compound.

379.   The method of Paragraph 373, 374, 375, 376, 377 or 378, wherein at least one strain in said plurality of cultures does not overexpress a gene product which is essential for proliferation of said organism.

380.   A method of profiling a compound's activity comprising:

performing the method of Paragraph 346 on a first culture using a first compound;

performing the method of Paragraph 346 on a second culture using a second compound; and

comparing the strains identified in said first culture to the strains identified in said second culture.

381.   A method of profiling a compound's activity comprising:

performing the method of Paragraph 347 on a first culture using a first compound;

performing the method of Paragraph 347 on a second culture using a second compound; and

comparing the strains identified in said first culture to the strains identified in said second culture.

382.   A method of profiling a compound's activity comprising:

performing the method of Paragraph 348 on a first culture using a first compound;

performing the method of Paragraph 348 on a second culture using a second compound; and

comparing the strains identified in said first culture to the strains identified in said second culture.

383.   A method of profiling a compound's activity comprising:

performing the method of Paragraph 349 on a first culture using a first compound;

performing the method of Paragraph 349 on a second culture using a second compound; and

comparing the strains identified in said first culture to the strains identified in said second culture.

5   384.   A method of profiling a compound's activity comprising:

performing the method of Paragraph 350 on a first culture using a first compound;

performing the method of Paragraph 350 on a second culture using a second compound; and

comparing the strains identified in said first culture to the strains identified in said

10 second culture.

385.   A method of profiling a compound's activity comprising:

performing the method of Paragraph 351 on a first culture using a first compound;

performing the method of Paragraph 351 on a second culture using a second compound; and

15 comparing the strains identified in said first culture to the strains identified in said second culture.

386.   A method of profiling a first compound's activity comprising:

growing an array of strains on a first solid medium comprising said first compound and on a second solid medium comprising a second compound, wherein each strain in said

20 array overexpresses a different gene product which is essential for proliferation of an organism, wherein said culture comprises a strain in which a gene product whose activity or level is inhibited by a nucleic acid comprising a nucleotide sequence selected from the group consisting of SEQ ID NOs.: 1-6213 is overexpressed, and wherein said first compound and said second compound inhibit the proliferation of said organism; and

25 comparing the pattern of strains which grow on said first solid medium with the pattern of strains which grow on said second solid medium.

387.   A method of profiling a first compound's activity comprising:

growing an array of strains on a first solid medium comprising said first compound and on a second solid medium comprising a second compound, wherein each strain in said

30 array overexpresses a different gene product which is essential for proliferation of an organism, wherein said culture comprises a strain in which a gene product encoded by a nucleic acid comprising a nucleotide sequence selected from the group consisting of SEQ ID NOs.: 6214-42397 is overexpressed, and wherein said first compound and said second compound inhibit the proliferation of said organism; and

35 comparing the pattern of strains which grow on said first solid medium with the pattern of strains which grow on said second solid medium.

388.   A method of profiling a first compound's activity comprising:

growing an array of strains on a first solid medium comprising said first compound and on a second solid medium comprising a second compound, wherein each strain in said array overexpresses a different gene product which is essential for proliferation of an organism, wherein said culture comprises a strain in which a gene product comprising an amino acid sequence selected from the group consisting of SEQ ID NOs.: 42938-78581 is overexpressed, and wherein said first compound and said second compound inhibit the proliferation of said organism; and

comparing the pattern of strains which grow on said first solid medium with the pattern of strains which grow on said second solid medium.

389.   A method of profiling a first compound's activity comprising:

growing an array of strains on a first solid medium comprising said first compound and on a second solid medium comprising a second compound, wherein each strain in said array overexpresses a different gene product which is essential for proliferation of an organism, wherein said culture comprises a strain in which a gene product selected from the group consisting of a gene product having at least 70% nucleotide sequence identity as determined using BLASTN version 2.0 with the default parameters to a gene product whose expression is inhibited by an antisense nucleic acid comprising a nucleotide sequence selected from the group consisting of SEQ ID NOs.: 1-6213, a gene product encoded by a nucleic acid having at least 70% nucleotide sequence identity as determined using BLASTN version 2.0 with the default parameters to a nucleic acid encoding a gene product whose expression is inhibited by an antisense nucleic acid comprising a nucleotide sequence selected from the group consisting of SEQ ID NOs: 1-6213, a gene product having at least 25% amino acid identity as determined using FASTA version 3.0t78 with the default parameters to a gene product whose expression is inhibited by an antisense nucleic acid comprising a nucleotide sequence selected from the group consisting of SEQ ID NOs.: 1-6213, a gene product encoded by a nucleic acid which hybridizes to a nucleic acid comprising a nucleotide sequence selected from the group consisting of SEQ ID NOs.: 1-6213 under stringent conditions, a gene product encoded by a nucleic acid which hybridizes to a nucleic acid comprising a nucleotide sequence selected from the group consisting of SEQ ID NOs.: 1-6213 under moderate conditions, and a gene product whose activity may be complemented by the gene product whose activity is inhibited by a nucleic acid comprising a nucleotide sequence selected from the group consisting of SEQ ID NOs: 1-6213 is overexpressed, and wherein said first compound and said second compound inhibit the proliferation of said organism; and

comparing the pattern of strains which grow on said first solid medium with the pattern of strains which grow on said second solid medium.

390.   A method of profiling a first compound's activity comprising:

growing an array of strains on a first solid medium comprising said first compound and on a second solid medium comprising a second compound, wherein each strain in said array overexpresses a different gene product which is essential for proliferation of an organism, wherein said culture comprises a strain in which a gene product encoded by a

5   nucleic acid comprising a nucleotide sequence selected from the group consisting of a nucleic acid comprising a nucleic acid having at least 70% nucleotide sequence identity as determined using BLASTN version 2.0 with the default parameters to a nucleotide sequence selected from the group consisting of SEQ ID NOS.: 6214-42397, a nucleic acid comprising a nucleotide sequence which hybridizes to a sequence selected from the group

10   consisting of SEQ ID NOS.: 6214-42397 under stringent conditions, and a nucleic acid comprising a nucleotide sequence which hybridizes to a nucleotide sequence selected from the group consisting of SEQ ID NOS.: 6214-42397 under moderate conditions is overexpressed, and wherein said first compound and said second compound inhibit the proliferation of said organism; and

15   comparing the pattern of strains which grow on said first solid medium with the pattern of strains which grow on said second solid medium.

391.   A method of profiling a first compound's activity comprising:

growing an array of strains on a first solid medium comprising said first compound and on a second solid medium comprising a second compound, wherein each strain in said

20   array overexpresses a different gene product which is essential for proliferation of an organism, wherein said culture comprises a strain in which a gene product comprises a polypeptide selected from the group consisting of a polypeptide having at least 25% amino acid identity as determined using FASTA version 3.0t78 to a polypeptide selected from the group consisting of SEQ ID NOs.: 42938-78581 and a polypeptide whose activity may be

25   complemented by a polypeptide selected from the group consisting of SEQ ID NOs: 42938-78581 is overexpressed, and wherein said first compound and said second compound inhibit the proliferation of said organism; and

comparing the pattern of strains which grow on said first solid medium with the pattern of strains which grow on said second solid medium.

30   392.   The method of any one of Paragraphs 380, 381, 382, 383, 384, 385, 386, 387, 388, 389, 390 or 391, wherein said first compound is present in a crude or partially purified state.

393.   A method for identifying the gene product on which a compound which inhibits proliferation of an organism acts comprising:

obtaining a culture comprising a plurality of strains wherein each strain

35   underexpresses a different gene product which is essential for proliferation of said organism, wherein said culture comprises a strain in which a gene product whose activity or level is inhibited by a nucleic acid comprising a nucleotide sequence selected from the group consisting of SEQ ID NOs.: 1-6213 is underexpressed;

contacting said culture with a sufficient concentration of said compound to inhibit the proliferation of strains of said organism which underexpress said gene product on which said compound acts, such that strains which underexpress said gene product on which said compound acts proliferate more slowly than strains which do not underexpress said gene

5   product on which said compound acts; and

identifying the gene product which is underexpressed in a strain which proliferated more slowly in said culture.

394.   A method for identifying the gene product on which a compound which inhibits proliferation of an organism acts comprising:

10   obtaining a culture comprising a plurality of strains wherein each strain underexpresses a different gene product which is essential for proliferation of said organism, wherein said culture comprises a strain in which a gene product encoded by a nucleic acid comprising a nucleotide sequence selected from the group consisting of SEQ ID NOs.: 6214-42397 is underexpressed;

15   contacting said culture with a sufficient concentration of said compound to inhibit the proliferation of strains of said organism which underexpress said gene product on which said compound acts, such that strains which underexpress said gene product on which said compound acts proliferate more slowly than strains which do not underexpress said gene product on which said compound acts; and

20   identifying the gene product which is underexpressed in a strain which proliferated more slowly in said culture.

395.   A method for identifying the gene product on which a compound which inhibits proliferation of an organism acts comprising:

obtaining a culture comprising a plurality of strains wherein each strain
25   underexpresses a different gene product which is essential for proliferation of said organism, wherein said culture comprises a strain in which a gene product comprising an amino acid sequence selected from the group consisting of SEQ ID NOs.: 42938-78581 is underexpressed;

contacting said culture with a sufficient concentration of said compound to inhibit
30   the proliferation of strains of said organism which underexpress said gene product on which said compound acts, such that strains which underexpress said gene product on which said compound acts proliferate more slowly than strains which do not underexpress said gene product on which said compound acts; and

identifying the gene product which is underexpressed in a strain which proliferated
35   more slowly in said culture.

396.   A method for identifying the gene product on which a compound which inhibits proliferation of an organism acts comprising:

obtaining a culture comprising a plurality of strains wherein each strain underexpresses a different gene product which is essential for proliferation of said organism, wherein said culture comprises a strain in which a gene product selected from the group consisting of a gene product having at least 70% nucleotide sequence identity as

5   determined using BLASTN version 2.0 with the default parameters to a gene product whose expression is inhibited by an antisense nucleic acid comprising a nucleotide sequence selected from the group consisting of SEQ ID NOs.: 1-6213, a gene product encoded by a nucleic acid having at least 70% nucleotide sequence identity as determined using BLASTN version 2.0 with the default parameters to a nucleic acid encoding a gene

10   product whose expression is inhibited by an antisense nucleic acid comprising a nucleotide sequence selected from the group consisting of SEQ ID NOs: 1-6213, a gene product having at least 25% amino acid identity as determined using FASTA version 3.0t78 with the default parameters to a gene product whose expression is inhibited by an antisense nucleic acid comprising a nucleotide sequence selected from the group consisting of SEQ

15   ID NOs.: 1-6213, a gene product encoded by a nucleic acid which hybridizes to a nucleic acid comprising a nucleotide sequence selected from the group consisting of SEQ ID NOs.: 1-6213 under stringent conditions, a gene product encoded by a nucleic acid which hybridizes to a nucleic acid comprising a nucleotide sequence selected from the group consisting of SEQ ID NOs.: 1-6213 under moderate conditions, and a gene product whose

20   activity may be complemented by the gene product whose activity is inhibited by a nucleic acid comprising a nucleotide sequence selected from the group consisting of SEQ ID NOs: 1-6213 is underexpressed;

       contacting said culture with a sufficient concentration of said compound to inhibit the proliferation of strains of said organism which underexpress said gene product on which

25   said compound acts, such that strains which underexpress said gene product on which said compound acts proliferate more slowly than strains which do not underexpress said gene product on which said compound acts; and

       identifying the gene product which is underexpressed in a strain which proliferated more slowly in said culture.

30   397.   A method for identifying the gene product on which a compound which inhibits proliferation of an organism acts comprising:

       obtaining a culture comprising a plurality of strains wherein each strain underexpresses a different gene product which is essential for proliferation of said organism, wherein said culture comprises a strain in which a gene product encoded by a

35   nucleic acid comprising a nucleotide sequence selected from the group consisting of a nucleic acid comprising a nucleic acid having at least 70% nucleotide sequence identity as determined using BLASTN version 2.0 with the default parameters to a nucleotide sequence selected from the group consisting of SEQ ID NOS.: 6214-42397, a nucleic acid

comprising a nucleotide sequence which hybridizes to a sequence selected from the group consisting of SEQ ID NOS.: 6214-42397 under stringent conditions, and a nucleic acid comprising a nucleotide sequence which hybridizes to a nucleotide sequence selected from the group consisting of SEQ ID NOS.: 6214-42397 under moderate conditions is underexpressed;

contacting said culture with a sufficient concentration of said compound to inhibit the proliferation of strains of said organism which underexpress said gene product on which said compound acts, such that strains which underexpress said gene product on which said compound acts proliferate more slowly than strains which do not underexpress said gene product on which said compound acts; and

identifying the gene product which is underexpressed in a strain which proliferated more slowly in said culture.

398. A method for identifying the gene product on which a compound which inhibits proliferation of an organism acts comprising:

obtaining a culture comprising a plurality of strains wherein each strain underexpresses a different gene product which is essential for proliferation of said organism, wherein said culture comprises a strain in which a gene product comprises a polypeptide selected from the group consisting of a polypeptide having at least 25% amino acid identity as determined using FASTA version 3.0t78 to a polypeptide selected from the group consisting of SEQ ID NOs.: 42938-78581 and a polypeptide whose activity may be complemented by a polypeptide selected from the group consisting of SEQ ID NOs: 42938-78581 is underexpressed;

contacting said culture with a sufficient concentration of said compound to inhibit the proliferation of strains of said organism which underexpress said gene product on which said compound acts, such that strains which underexpress said gene product on which said compound acts proliferate more slowly than strains which do not underexpress said gene product on which said compound acts; and

identifying the gene product which is underexpressed in a strain which proliferated more slowly in said culture.

399. The method of Paragraph 393, 394, 395, 396, 397 or 398, wherein at least one strain in said culture does not underexpresses a gene product which is essential for proliferation of said organism.

400. The method of Paragraph 393, 394, 395, 396, 397 or 398, wherein said strains which underexpresess said gene products comprise a nucleic acid complementary to at least a portion of a gene encoding said gene product which is essential for proliferation of said organism operably linked to a regulatable promoter.

401. The method of Paragraph 393, 394, 395, 396, 397 or 398, wherein said strains which underexpress said gene products express an antisense nucleic acid complementary to at least

a portion of a gene encoding said gene product which is essential for proliferation of said organism, wherein expression of said antisense nucleic acid reduces expression of said gene product in said strain.

402.   The method of Paragraph 393, 394, 395, 396, 397 or 398, wherein said identification step comprises determining the nucleotide sequence of a nucleic acid encoding said gene product in said strain which proliferated more slowly.

403.   The method of Paragraph 393, 394, 395, 396, 397 or 398, wherein said identification step comprises performing an amplification reaction to identify the nucleic acid encoding said gene product in said cell which proliferated more slowly.

404.   The method of Paragraph 393, 394, 395, 396, 397 or 398, wherein the products of said amplification reaction are labeled with a detectable dye.

405.   The method of Paragraph 404, wherein said identification step comprises performing a hybridization procedure.

406.   The method of Paragraph 393, 394, 395, 396, 397 or 398, wherein said identification step comprises contacting a nucleic acid array with a nucleic acid encoding said gene product in said cell which proliferated more slowly.

407.   The method of Paragraph 393, 394, 395, 396, 397 or 398, wherein said organism is selected from the group consisting of bacteria, fungi, protozoa.

408.   The method of Paragraph 393, 394, 395, 396, 397 or 398, wherein said culture is a culture of an organism selected from the group consisting of *Acinetobacter baumannii, Anaplasma marginale, Aspergillus fumigatus, Bacillus anthracis, Bacteroides fragilis, Bordetella pertussis, Borrelia burgdorferi, Burkholderia cepacia, Burkholderia fungorum, Burkholderia mallei, Campylobacter jejuni, Candida albicans, Candida glabrata* (also called *Torulopsis glabrata*), *Candida tropicalis, Candida parapsilosis, Candida guilliermondii, Candida krusei, Candida kefyr* (also called *Candida pseudotropicalis*), *Candida dubliniensis, Chlamydia pneumoniae, Chlamydia trachomatis, Clostridium acetobutylicum, Clostridium botulinum, Clostridium difficile, Clostridium perfringens, Coccidioides immitis, Corynebacterium diptheriae, Cryptococcus neoformans, Enterobacter cloacae, Enterococcus faecalis, Enterococcus faecium, Escherichia coli, Haemophilus influenzae, Helicobacter pylori, Histoplasma capsulatum, Klebsiella pneumoniae, Legionella pneumophila, Listeria monocytogenes, Moraxella catarrhalis, Mycobacterium avium, Mycobacterium bovis, Mycobacterium leprae, Mycobacterium tuberculosis, Mycoplasma genitalium, Mycoplasma pneumoniae, Neisseria gonorrhoeae, Neisseria meningitidis, Nocardia asteroides, Pasteurella haemolytica, Pasteurella multocida, Pneumocystis carinii, Proteus mirabilis, Proteus vulgaris, Pseudomonas aeruginosa, Pseudomonas putida, Pseudomonas syringae, Salmonella bongori, Salmonella cholerasuis, Salmonella enterica, Salmonella paratyphi, Salmonella typhi, Salmonella typhimurium, Shigella boydii, Shigella dysenteriae, Shigella flexneri, Shigella sonnei, Staphylococcus aureus, Staphylococcus epidermidis, Staphylococcus haemolyticus, Streptococcus pneumoniae, Streptococcus mutans, Streptococcus pyogenes, Treponema pallidum,*

Ureaplasma urealyticum, Vibrio cholerae, Vibrio parahaemolyticus, Vibrio vulnificans, Yersinia enterocolitica, Yersinia pestis and any species falling within the genera of any of the above species.

409.   The method of Paragraph 393, 394, 395, 396, 397 or 398, wherein said compound is obtained from a library of natural compounds.

410.   The method of Paragraph 393, 394, 395, 396, 397 or 398, wherein said compound is obtained from a library of synthetic compounds.

411.   The method of Paragraph 393, 394, 395, 396, 397 or 398, wherein said compound is present in a crude or partially purified state.

412.   The method of Paragraph 393, 394, 395, 396, 397 or 398, further comprising determining whether said gene product in said strain which proliferated more slowly in said culture has a counterpart in at least one other organism.

413.   A method for identifying the gene product on which a compound which inhibits proliferation of an organism acts comprising:

obtaining a plurality of cultures, each culture comprising a plurality of strains wherein each strain underexpresses a different gene product which is essential for proliferation of said organism, wherein said culture comprises a strain in which a gene product whose activity or level is inhibited by a nucleic acid comprising a nucleotide sequence selected from the group consisting of SEQ ID NOs.: 1-6213 is underexpressed;

contacting each of said cultures with a different concentration of said compound; and

identifying the gene product which is underexpressed in a strain whose rate of proliferation is reduced by said compound.

414.   A method for identifying the gene product on which a compound which inhibits proliferation of an organism acts comprising:

obtaining a plurality of cultures, each culture comprising a plurality of strains wherein each strain underexpresses a different gene product which is essential for proliferation of said organism, wherein said culture comprises a strain in which a gene product encoded by a nucleic acid comprising a nucleotide sequence selected from the group consisting of SEQ ID NOs.: 6214-42397 is underexpressed;

contacting each of said cultures with a different concentration of said compound; and

identifying the gene product which is underexpressed in a strain whose rate of proliferation is reduced by said compound.

415.   A method for identifying the gene product on which a compound which inhibits proliferation of an organism acts comprising:

obtaining a plurality of cultures, each culture comprising a plurality of strains wherein each strain underexpresses a different gene product which is essential for proliferation of said organism, wherein said culture comprises a strain in which a gene

product comprising an amino acid sequence selected from the group consisting of SEQ ID NOs.: 42938-78581 is underexpressed;

contacting each of said cultures with a different concentration of said compound; and

5   identifying the gene product which is underexpressed in a strain whose rate of proliferation is reduced by said compound.

416.   A method for identifying the gene product on which a compound which inhibits proliferation of an organism acts comprising:

obtaining a plurality of cultures, each culture comprising a plurality of strains

10   wherein each strain underexpresses a different gene product which is essential for proliferation of said organism, wherein said culture comprises a strain in which a gene product selected from the group consisting of a gene product having at least 70% nucleotide sequence identity as determined using BLASTN version 2.0 with the default parameters to a gene product whose expression is inhibited by an antisense nucleic acid comprising a

15   nucleotide sequence selected from the group consisting of SEQ ID NOs.: 1-6213, a gene product encoded by a nucleic acid having at least 70% nucleotide sequence identity as determined using BLASTN version 2.0 with the default parameters to a nucleic acid encoding a gene product whose expression is inhibited by an antisense nucleic acid comprising a nucleotide sequence selected from the group consisting of SEQ ID NOs: 1-

20   6213, a gene product having at least 25% amino acid identity as determined using FASTA version 3.0t78 with the default parameters to a gene product whose expression is inhibited by an antisense nucleic acid comprising a nucleotide sequence selected from the group consisting of SEQ ID NOs.: 1-6213, a gene product encoded by a nucleic acid which hybridizes to a nucleic acid comprising a nucleotide sequence selected from the group

25   consisting of SEQ ID NOs.: 1-6213 under stringent conditions, a gene product encoded by a nucleic acid which hybridizes to a nucleic acid comprising a nucleotide sequence selected from the group consisting of SEQ ID NOs.: 1-6213 under moderate conditions, and a gene product whose activity may be complemented by the gene product whose activity is inhibited by a nucleic acid comprising a nucleotide sequence selected from the group

30   consisting of SEQ ID NOs: 1-6213 is underexpressed;

contacting each of said cultures with a different concentration of said compound; and

identifying the gene product which is underexpressed in a strain whose rate of proliferation is reduced by said compound.

35   417.   A method for identifying the gene product on which a compound which inhibits proliferation of an organism acts comprising:

obtaining a plurality of cultures, each culture comprising a plurality of strains wherein each strain underexpresses a different gene product which is essential for

proliferation of said organism, wherein said culture comprises a strain in which a gene product encoded by a nucleic acid comprising a nucleotide sequence selected from the group consisting of a nucleic acid comprising a nucleic acid having at least 70% nucleotide sequence identity as determined using BLASTN version 2.0 with the default parameters to

5   a nucleotide sequence selected from the group consisting of SEQ ID NOS.: 6214-42397, a nucleic acid comprising a nucleotide sequence which hybridizes to a sequence selected from the group consisting of SEQ ID NOS.: 6214-42397 under stringent conditions, and a nucleic acid comprising a nucleotide sequence which hybridizes to a nucleotide sequence selected from the group consisting of SEQ ID NOS.: 6214-42397 under moderate

10   conditions is underexpressed;

contacting each of said cultures with a different concentration of said compound; and

identifying the gene product which is underexpressed in a strain whose rate of proliferation is reduced by said compound.

15   418.   A method for identifying the gene product on which a compound which inhibits proliferation of an organism acts comprising:

obtaining a plurality of cultures, each culture comprising a plurality of strains wherein each strain underexpresses a different gene product which is essential for proliferation of said organism, wherein said culture comprises a strain in which a gene

20   product comprises a polypeptide selected from the group consisting of a polypeptide having at least 25% amino acid identity as determined using FASTA version 3.0t78 to a polypeptide selected from the group consisting of SEQ ID NOs.: 42938-78581 and a polypeptide whose activity may be complemented by a polypeptide selected from the group consisting of SEQ ID NOs: 42938-78581 is underexpressed;

25   contacting each of said cultures with a different concentration of said compound; and

identifying the gene product which is underexpressed in a strain whose rate of proliferation is reduced by said compound.

419.   A method of profiling a compound's activity comprising:

30   performing the method of Paragraph 393 on a first culture using a first compound;

performing the method of Paragraph 393 on a second culture using a second compound; and

comparing the strains identified in said first culture to the strains identified in said second culture.

35   420.   A method of profiling a compound's activity comprising:

performing the method of Paragraph 394 on a first culture using a first compound;

performing the method of Paragraph 394 on a second culture using a second compound; and

comparing the strains identified in said first culture to the strains identified in said second culture.

421.   A method of profiling a compound's activity comprising:

performing the method of Paragraph 395 on a first culture using a first compound;

performing the method of Paragraph 395 on a second culture using a second compound; and

comparing the strains identified in said first culture to the strains identified in said second culture.

422.   A method of profiling a compound's activity comprising

performing the method of Paragraph 396 on a first culture using a first compound;

performing the method of Paragraph 396 on a second culture using a second compound; and

comparing the strains identified in said first culture to the strains identified in said second culture.

423.   A method of profiling a compound's activity comprising

performing the method of Paragraph 397 on a first culture using a first compound;

performing the method of Paragraph 397 on a second culture using a second compound; and

comparing the strains identified in said first culture to the strains identified in said second culture.

424.   A method of profiling a compound's activity comprising

performing the method of Paragraph 398 on a first culture using a first compound;

performing the method of Paragraph 398 on a second culture using a second compound; and

comparing the strains identified in said first culture to the strains identified in said second culture.

425.   A method of profiling a first compound's activity comprising:

growing an array of strains on a first solid medium comprising said first compound and on a second solid medium comprising a second compound, wherein said array comprises a plurality of strains wherein each strain underexpresses a different gene product which is essential for proliferation of an organism, wherein said culture comprises a strain in which a gene product whose activity or level is inhibited by a nucleic acid comprising a nucleotide sequence selected from the group consisting of SEQ ID NOs.: 1-6213 is underexpressed, and wherein said first compound and said second compound inhibit the proliferation of said organism; and

comparing the pattern of strains which grow on said first solid medium with the pattern of strains which grow on said second solid medium.

426.   A method of profiling a first compound's activity comprising:

growing an array of strains on a first solid medium comprising said first compound and on a second solid medium comprising a second compound, wherein said array comprises a plurality of strains wherein each strain underexpresses a different gene product which is essential for proliferation of an organism, wherein said culture comprises a strain

5   in which a gene product encoded by a nucleic acid comprising a nucleotide sequence selected from the group consisting of SEQ ID NOs.: 6214-42397 is underexpressed, and wherein said first compound and said second compound inhibit the proliferation of said organism; and

comparing the pattern of strains which grow on said first solid medium with the

10   pattern of strains which grow on said second solid medium.

427.   A method of profiling a first compound's activity comprising:

growing an array of strains on a first solid medium comprising said first compound and on a second solid medium comprising a second compound, wherein said array comprises a plurality of strains wherein each strain underexpresses a different gene product

15   which is essential for proliferation of an organism, wherein said culture comprises a strain in which a gene product comprising an amino acid sequence selected from the group consisting of SEQ ID NOs.: 42938-78581 is underexpressed, and wherein said first compound and said second compound inhibit the proliferation of said organism; and

comparing the pattern of strains which grow on said first solid medium with the

20   pattern of strains which grow on said second solid medium.

428.   A method of profiling a first compound's activity comprising:

growing an array of strains on a first solid medium comprising said first compound and on a second solid medium comprising a second compound, wherein said array comprises a plurality of strains wherein each strain underexpresses a different gene product

25   which is essential for proliferation of an organism, wherein said culture comprises a strain in which a gene product selected from the group consisting of a gene product having at least 70% nucleotide sequence identity as determined using BLASTN version 2.0 with the default parameters to a gene product whose expression is inhibited by an antisense nucleic acid comprising a nucleotide sequence selected from the group consisting of SEQ ID NOs.:

30   1-6213, a gene product encoded by a nucleic acid having at least 70% nucleotide sequence identity as determined using BLASTN version 2.0 with the default parameters to a nucleic acid encoding a gene product whose expression is inhibited by an antisense nucleic acid comprising a nucleotide sequence selected from the group consisting of SEQ ID NOs: 1-6213, a gene product having at least 25% amino acid identity as determined using FASTA

35   version 3.0t78 with the default parameters to a gene product whose expression is inhibited by an antisense nucleic acid comprising a nucleotide sequence selected from the group consisting of SEQ ID NOs.: 1-6213, a gene product encoded by a nucleic acid which hybridizes to a nucleic acid comprising a nucleotide sequence selected from the group

consisting of SEQ ID NOs.: 1-6213 under stringent conditions, a gene product encoded by a nucleic acid which hybridizes to a nucleic acid comprising a nucleotide sequence selected from the group consisting of SEQ ID NOs.: 1-6213 under moderate conditions, and a gene product whose activity may be complemented by the gene product whose activity is

5   inhibited by a nucleic acid comprising a nucleotide sequence selected from the group consisting of SEQ ID NOs: 1-6213 is underexpressed, and wherein said first compound and said second compound inhibit the proliferation of said organism; and

comparing the pattern of strains which grow on said first solid medium with the pattern of strains which grow on said second solid medium.

10   429.   A method of profiling a first compound's activity comprising:

growing an array of strains on a first solid medium comprising said first compound and on a second solid medium comprising a second compound, wherein said array comprises a plurality of strains wherein each strain underexpresses a different gene product which is essential for proliferation of an organism , wherein said culture comprises a strain

15   in which a gene product encoded by a nucleic acid comprising a nucleotide sequence selected from the group consisting of a nucleic acid comprising a nucleic acid having at least 70% nucleotide sequence identity as determined using BLASTN version 2.0 with the default parameters to a nucleotide sequence selected from the group consisting of SEQ ID NOS.: 6214-42397, a nucleic acid comprising a nucleotide sequence which hybridizes to a

20   sequence selected from the group consisting of SEQ ID NOS.: 6214-42397 under stringent conditions, and a nucleic acid comprising a nucleotide sequence which hybridizes to a nucleotide sequence selected from the group consisting of SEQ ID NOS.: 6214-42397 under moderate conditions is underexpressed, and wherein said first compound and said second compound inhibit the proliferation of said organism; and

25   comparing the pattern of strains which grow on said first solid medium with the pattern of strains which grow on said second solid medium.

430.   A method of profiling a first compound's activity comprising:

growing an array of strains on a first solid medium comprising said first compound and on a second solid medium comprising a second compound, wherein said array

30   comprises a plurality of strains wherein each strain underexpresses a different gene product which is essential for proliferation of an organism, wherein said culture comprises a strain in which a gene product comprises a polypeptide selected from the group consisting of a polypeptide having at least 25% amino acid identity as determined using FASTA version 3.0t78 to a polypeptide selected from the group consisting of SEQ ID NOs.: 42938-78581

35   and a polypeptide whose activity may be complemented by a polypeptide selected from the group consisting of SEQ ID NOs: 42938-78581 is underexpressed, and wherein said first compound and said second compound inhibit the proliferation of said organism; and

comparing the pattern of strains which grow on said first solid medium with the pattern of strains which grow on said second solid medium.

431.   The method of any one of Paragraphs 419, 420, 421, 422, 423, 424, 425, 426, 427, 428, 429 or 430, wherein said first compound is present in a crude or partially purified state.

432.   A method for identifying the gene product on which a compound which inhibits proliferation of an organism acts comprising:

obtaining a plurality of cultures comprising a plurality of strains wherein each strain underexpresses a different gene product which is essential for proliferation of said organism, wherein said culture comprises a strain in which a gene product whose activity or level is inhibited by a nucleic acid comprising a nucleotide sequence selected from the group consisting of SEQ ID NOs.: 1-6213 is underexpressed;

contacting each of said plurality of cultures with a varying concentration of a regulatory agent which regulates the level of expression of said gene products which are essential for proliferation of said organism; and

identifying the gene product which is underexpressed in a strain whose rate of proliferation is reduced by said compound.

433.   A method for identifying the gene product on which a compound which inhibits proliferation of an organism acts comprising:

obtaining a plurality of cultures comprising a plurality of strains wherein each strain underexpresses a different gene product which is essential for proliferation of said organism, wherein said culture comprises a strain in which a gene product encoded by a nucleic acid comprising a nucleotide sequence selected from the group consisting of SEQ ID NOs.: 6214-42397 is underexpressed;

contacting each of said plurality of cultures with a varying concentration of a regulatory agent which regulates the level of expression of said gene products which are essential for proliferation of said organism; and

identifying the gene product which is underexpressed in a strain whose rate of proliferation is reduced by said compound.

434.   A method for identifying the gene product on which a compound which inhibits proliferation of an organism acts comprising:

obtaining a plurality of cultures comprising a plurality of strains wherein each strain underexpresses a different gene product which is essential for proliferation of said organism, wherein said culture comprises a strain in which a gene product comprising an amino acid sequence selected from the group consisting of SEQ ID NOs.: 42938-78581 is underexpressed;

contacting each of said plurality of cultures with a varying concentration of a regulatory agent which regulates the level of expression of said gene products which are essential for proliferation of said organism; and

identifying the gene product which is underexpressed in a strain whose rate of proliferation is reduced by said compound.

435.   A method for identifying the gene product on which a compound which inhibits proliferation of an organism acts comprising:

5   obtaining a plurality of cultures comprising a plurality of strains wherein each strain underexpresses a different gene product which is essential for proliferation of said organism, wherein said culture comprises a strain in which a gene product selected from the group consisting of a gene product having at least 70% nucleotide sequence identity as determined using BLASTN version 2.0 with the default parameters to a gene product

10   whose expression is inhibited by an antisense nucleic acid comprising a nucleotide sequence selected from the group consisting of SEQ ID NOs.: 1-6213, a gene product encoded by a nucleic acid having at least 70% nucleotide sequence identity as determined using BLASTN version 2.0 with the default parameters to a nucleic acid encoding a gene product whose expression is inhibited by an antisense nucleic acid comprising a nucleotide

15   sequence selected from the group consisting of SEQ ID NOs: 1-6213, a gene product having at least 25% amino acid identity as determined using FASTA version 3.0t78 with the default parameters to a gene product whose expression is inhibited by an antisense nucleic acid comprising a nucleotide sequence selected from the group consisting of SEQ ID NOs.: 1-6213, a gene product encoded by a nucleic acid which hybridizes to a nucleic

20   acid comprising a nucleotide sequence selected from the group consisting of SEQ ID NOs.: 1-6213 under stringent conditions, a gene product encoded by a nucleic acid which hybridizes to a nucleic acid comprising a nucleotide sequence selected from the group consisting of SEQ ID NOs.: 1-6213 under moderate conditions, and a gene product whose activity may be complemented by the gene product whose activity is inhibited by a nucleic

25   acid comprising a nucleotide sequence selected from the group consisting of SEQ ID NOs: 1-6213 is underexpressed;

contacting each of said plurality of cultures with a varying concentration of a regulatory agent which regulates the level of expression of said gene products which are essential for proliferation of said organism; and

30   identifying the gene product which is underexpressed in a strain whose rate of proliferation is reduced by said compound.

436.   A method for identifying the gene product on which a compound which inhibits proliferation of an organism acts comprising:

obtaining a plurality of cultures comprising a plurality of strains wherein each

35   strain underexpresses a different gene product which is essential for proliferation of said organism, wherein said culture comprises a strain in which a gene product encoded by a nucleic acid comprising a nucleotide sequence selected from the group consisting of a nucleic acid comprising a nucleic acid having at least 70% nucleotide sequence identity as

determined using BLASTN version 2.0 with the default parameters to a nucleotide sequence selected from the group consisting of SEQ ID NOS.: 6214-42397, a nucleic acid comprising a nucleotide sequence which hybridizes to a sequence selected from the group consisting of SEQ ID NOS.: 6214-42397 under stringent conditions, and a nucleic acid

5   comprising a nucleotide sequence which hybridizes to a nucleotide sequence selected from the group consisting of SEQ ID NOS.: 6214-42397 under moderate conditions is underexpressed;

contacting each of said plurality of cultures with a varying concentration of a regulatory agent which regulates the level of expression of said gene products which are

10   essential for proliferation of said organism; and

identifying the gene product which is underexpressed in a strain whose rate of proliferation is reduced by said compound.

437.   A method for identifying the gene product on which a compound which inhibits proliferation of an organism acts comprising:

15   obtaining a plurality of cultures comprising a plurality of strains wherein each strain underexpresses a different gene product which is essential for proliferation of said organism, wherein said culture comprises a strain in which a gene product comprises a polypeptide selected from the group consisting of a polypeptide having at least 25% amino acid identity as determined using FASTA version 3.0t78 to a polypeptide selected from the

20   group consisting of SEQ ID NOs.: 42938-78581 and a polypeptide whose activity may be complemented by a polypeptide selected from the group consisting of SEQ ID NOs: 42938-78581 is underexpressed;

contacting each of said plurality of cultures with a varying concentration of a regulatory agent which regulates the level of expression of said gene products which are

25   essential for proliferation of said organism; and

identifying the gene product which is underexpressed in a strain whose rate of proliferation is reduced by said compound.

438.   A culture comprising a plurality of strains wherein each strain overexpresses a different gene product which is essential for proliferation of said organism, wherein said culture

30   comprises a strain in which a gene product whose activity or level is inhibited by a nucleic acid comprising a nucleotide sequence selected from the group consisting of SEQ ID NOs.: 1-6213 is overexpressed.

439.   A culture comprising a plurality of strains wherein each strain overexpresses a different gene product which is essential for proliferation of said organism, wherein said culture

35   comprises a strain in which a gene product encoded by a nucleic acid comprising a nucleotide sequence selected from the group consisting of SEQ ID NOs.: 6214-42397 is overexpressed.

440.   A culture comprising a plurality of strains wherein each strain overexpresses a different gene product which is essential for proliferation of said organism, wherein said culture

comprises a strain in which a gene product comprising an amino acid sequence selected from the group consisting of SEQ ID NOs.: 42938-78581 is overexpressed.

441.   A culture comprising a plurality of strains wherein each strain overexpresses a different gene product which is essential for proliferation of said organism, wherein said culture

5   comprises a strain in which a gene product selected from the group consisting of a gene product having at least 70% nucleotide sequence identity as determined using BLASTN version 2.0 with the default parameters to a gene product whose expression is inhibited by an antisense nucleic acid comprising a nucleotide sequence selected from the group consisting of SEQ ID NOs.: 1-6213, a gene product encoded by a nucleic acid having at least 70% nucleotide sequence identity as

10   determined using BLASTN version 2.0 with the default parameters to a nucleic acid encoding a gene product whose expression is inhibited by an antisense nucleic acid comprising a nucleotide sequence selected from the group consisting of SEQ ID NOs: 1-6213, a gene product having at least 25% amino acid identity as determined using FASTA version 3.0t78 with the default parameters to a gene product whose expression is inhibited by an antisense nucleic acid comprising a nucleotide

15   sequence selected from the group consisting of SEQ ID NOs.: 1-6213, a gene product encoded by a nucleic acid which hybridizes to a nucleic acid comprising a nucleotide sequence selected from the group consisting of SEQ ID NOs.: 1-6213 under stringent conditions, a gene product encoded by a nucleic acid which hybridizes to a nucleic acid comprising a nucleotide sequence selected from the group consisting of SEQ ID NOs.: 1-6213 under moderate conditions, and a gene product whose

20   activity may be complemented by the gene product whose activity is inhibited by a nucleic acid comprising a nucleotide sequence selected from the group consisting of SEQ ID NOs: 1-6213 is overexpressed.

442.   A culture comprising a plurality of strains wherein each strain overexpresses a different gene product which is essential for proliferation of said organism, wherein said culture

25   comprises a strain in which a gene product encoded by a nucleic acid comprising a nucleotide sequence selected from the group consisting of a nucleic acid comprising a nucleic acid having at least 70% nucleotide sequence identity as determined using BLASTN version 2.0 with the default parameters to a nucleotide sequence selected from the group consisting of SEQ ID NOS.: 6214-42397, a nucleic acid comprising a nucleotide sequence which hybridizes to a sequence selected

30   from the group consisting of SEQ ID NOS.: 6214-42397 under stringent conditions, and a nucleic acid comprising a nucleotide sequence which hybridizes to a nucleotide sequence selected from the group consisting of SEQ ID NOS.: 6214-42397 under moderate conditions is overexpressed.

443.   A culture comprising a plurality of strains wherein each strain overexpresses a different gene product which is essential for proliferation of said organism, wherein said culture

35   comprises a strain in which a gene product comprises a polypeptide selected from the group consisting of a polypeptide having at least 25% amino acid identity as determined using FASTA version 3.0t78 to a polypeptide selected from the group consisting of SEQ ID NOs.: 42938-78581

and a polypeptide whose activity may be complemented by a polypeptide selected from the group consisting of SEQ ID NOs: 42938-78581 is overexpressed.

444.   The culture of Paragraph 438, 439, 440, 441, 442 or 443, wherein said strains which overexpresess said gene products comprise a nucleic acid encoding said gene product which is essential for proliferation of said organism operably linked to a regulatable promoter.

445.   The culture of Paragraph 438, 439, 440, 441, 442 or 443, wherein said strains which overexpresess said gene products comprise a nucleic acid encoding said gene product which is essential for proliferation of said organism operably linked to a constitutive promoter.

446.   The culture of Paragraph 438, 439, 440, 441, 442 or 443, wherein said culture is a culture of an organism selected from the group consisting of *Acinetobacter baumannii, Anaplasma marginale, Aspergillus fumigatus, Bacillus anthracis, Bacteroides fragilis, Bordetella pertussis, Borrelia burgdorferi, Burkholderia cepacia, Burkholderia fungorum, Burkholderia mallei, Campylobacter jejuni, Candida albicans, Candida glabrata* (also called *Torulopsis glabrata), Candida tropicalis, Candida parapsilosis, Candida guilliermondii, Candida krusei, Candida kefyr* (also called *Candida pseudotropicalis), Candida dubliniensis, Chlamydia pneumoniae, Chlamydia trachomatis, Clostridium acetobutylicum, Clostridium botulinum, Clostridium difficile, Clostridium perfringens, Coccidioides immitis, Corynebacterium diptheriae, Cryptococcus neoformans, Enterobacter cloacae, Enterococcus faecalis, Enterococcus faecium, Escherichia coli, Haemophilus influenzae, Helicobacter pylori, Histoplasma capsulatum, Klebsiella pneumoniae, Legionella pneumophila, Listeria monocytogenes, Moraxella catarrhalis, Mycobacterium avium, Mycobacterium bovis, Mycobacterium leprae, Mycobacterium tuberculosis, Mycoplasma genitalium, Mycoplasma pneumoniae, Neisseria gonorrhoeae, Neisseria meningitidis, Nocardia asteroides, Pasteurella haemolytica, Pasteurella multocida, Pneumocystis carinii, Proteus mirabilis, Proteus vulgaris, Pseudomonas aeruginosa, Pseudomonas putida, Pseudomonas syringae, Salmonella bongori, Salmonella cholerasuis, Salmonella enterica, Salmonella paratyphi, Salmonella typhi, Salmonella typhimurium, Shigella boydii, Shigella dysenteriae, Shigella flexneri, Shigella sonnei, Staphylococcus aureus, Staphylococcus epidermidis, Staphylococcus haemolyticus, Streptococcus pneumoniae, Streptococcus mutans, Streptococcus pyogenes, Treponema pallidum, Ureaplasma urealyticum, Vibrio cholerae, Vibrio parahaemolyticus, Vibrio vulnificans, Yersinia enterocolitica, Yersinia pestis* and any species falling within the genera of any of the above species.

447.   A culture comprising a a plurality of strains wherein each strain underexpresses a different gene product which is essential for proliferation of said organism, wherein said culture comprises a strain in which a gene product whose activity or level is inhibited by a nucleic acid comprising a nucleotide sequence selected from the group consisting of SEQ ID NOs.: 1-6213 is underexpressed.

448.   A culture comprising a a plurality of strains wherein each strain underexpresses a different gene product which is essential for proliferation of said organism, wherein said culture

comprises a strain in which a gene product encoded by a nucleic acid comprising a nucleotide sequence selected from the group consisting of SEQ ID NOs.: 6214-42397 is underexpressed.

449.   A culture comprising a a plurality of strains wherein each strain underexpresses a different gene product which is essential for proliferation of said organism, wherein said culture

5   comprises a strain in which a gene product comprising an amino acid sequence selected from the group consisting of SEQ ID NOs.: 42938-78581 is underexpressed.

450.   A culture comprising a a plurality of strains wherein each strain underexpresses a different gene product which is essential for proliferation of said organism, wherein said culture comprises a strain in which a gene product selected from the group consisting of a gene product

10   having at least 70% nucleotide sequence identity as determined using BLASTN version 2.0 with the default parameters to a gene product whose expression is inhibited by an antisense nucleic acid comprising a nucleotide sequence selected from the group consisting of SEQ ID NOs.: 1-6213, a gene product encoded by a nucleic acid having at least 70% nucleotide sequence identity as determined using BLASTN version 2.0 with the default parameters to a nucleic acid encoding a

15   gene product whose expression is inhibited by an antisense nucleic acid comprising a nucleotide sequence selected from the group consisting of SEQ ID NOs: 1-6213, a gene product having at least 25% amino acid identity as determined using FASTA version 3.0t78 with the default parameters to a gene product whose expression is inhibited by an antisense nucleic acid comprising a nucleotide sequence selected from the group consisting of SEQ ID NOs.: 1-6213, a gene product encoded by a

20   nucleic acid which hybridizes to a nucleic acid comprising a nucleotide sequence selected from the group consisting of SEQ ID NOs.: 1-6213 under stringent conditions, a gene product encoded by a nucleic acid which hybridizes to a nucleic acid comprising a nucleotide sequence selected from the group consisting of SEQ ID NOs.: 1-6213 under moderate conditions, and a gene product whose activity may be complemented by the gene product whose activity is inhibited by a nucleic acid

25   comprising a nucleotide sequence selected from the group consisting of SEQ ID NOs: 1-6213 is underexpressed.

451.   A culture comprising a a plurality of strains wherein each strain underexpresses a different gene product which is essential for proliferation of said organism, wherein said culture comprises a strain in which a gene product encoded by a nucleic acid comprising a nucleotide

30   sequence selected from the group consisting of a nucleic acid comprising a nucleic acid having at least 70% nucleotide sequence identity as determined using BLASTN version 2.0 with the default parameters to a nucleotide sequence selected from the group consisting of SEQ ID NOS.: 6214-42397, a nucleic acid comprising a nucleotide sequence which hybridizes to a sequence selected from the group consisting of SEQ ID NOS.: 6214-42397 under stringent conditions, and a nucleic

35   acid comprising a nucleotide sequence which hybridizes to a nucleotide sequence selected from the group consisting of SEQ ID NOS.: 6214-42397 under moderate conditions is underexpressed.

452.   A culture comprising a a plurality of strains wherein each strain underexpresses a different gene product which is essential for proliferation of said organism, wherein said culture

comprises a strain in which a gene product comprises a polypeptide selected from the group consisting of a polypeptide having at least 25% amino acid identity as determined using FASTA version 3.0t78 to a polypeptide selected from the group consisting of SEQ ID NOs.: 42938-78581 and a polypeptide whose activity may be complemented by a polypeptide selected from the group consisting of SEQ ID NOs: 42938-78581 is underexpressed.

453.   The culture of Paragraph 447, 448, 449, 450, 451 or 452, wherein said strains which underexpress said gene products comprise a nucleic acid encoding said gene product which is essential for proliferation of said organism operably linked to a regulatable promoter.

454.   The culture of Paragraph 447, 448, 449, 450, 451 or 452, wherein said strains which underexpress said gene products comprise a nucleic acid encoding said gene product which is essential for proliferation of said organism operably linked to a constitutive promoter.

455.   The culture of Paragraph 447, 448, 449, 450, 451 or 452, wherein said culture is a culture of an organism selected from the group consisting of *Acinetobacter baumannii, Anaplasma marginale, Aspergillus fumigatus, Bacillus anthracis, Bacteroides fragilis, Bordetella pertussis, Borrelia burgdorferi, Burkholderia cepacia, Burkholderia fungorum, Burkholderia mallei, Campylobacter jejuni, Candida albicans, Candida glabrata* (also called *Torulopsis glabrata*), *Candida tropicalis, Candida parapsilosis, Candida guilliermondii, Candida krusei, Candida kefyr* (also called *Candida pseudotropicalis*), *Candida dubliniensis, Chlamydia pneumoniae, Chlamydia trachomatis, Clostridium acetobutylicum, Clostridium botulinum, Clostridium difficile, Clostridium perfringens, Coccidioides immitis, Corynebacterium diptheriae, Cryptococcus neoformans, Enterobacter cloacae, Enterococcus faecalis, Enterococcus faecium, Escherichia coli, Haemophilus influenzae, Helicobacter pylori, Histoplasma capsulatum, Klebsiella pneumoniae, Legionella pneumophila, Listeria monocytogenes, Moraxella catarrhalis, Mycobacterium avium, Mycobacterium bovis, Mycobacterium leprae, Mycobacterium tuberculosis, Mycoplasma genitalium, Mycoplasma pneumoniae, Neisseria gonorrhoeae, Neisseria meningitidis, Nocardia asteroides, Pasteurella haemolytica, Pasteurella multocida, Pneumocystis carinii, Proteus mirabilis, Proteus vulgaris, Pseudomonas aeruginosa, Pseudomonas putida, Pseudomonas syringae, Salmonella bongori, Salmonella cholerasuis, Salmonella enterica, Salmonella paratyphi, Salmonella typhi, Salmonella typhimurium, Shigella boydii, Shigella dysenteriae, Shigella flexneri, Shigella sonnei, Staphylococcus aureus, Staphylococcus epidermidis, Staphylococcus haemolyticus, Streptococcus pneumoniae, Streptococcus mutans, Streptococcus pyogenes, Treponema pallidum, Ureaplasma urealyticum, Vibrio cholerae, Vibrio parahaemolyticus, Vibrio vulnificans, Yersinia enterocolitica, Yersinia pestis* and any species falling within the genera of any of the above species.

456.   A method for identifying the gene product on which a compound which inhibits proliferation of an organism acts comprising:

obtaining a culture comprising a plurality of strains wherein each strain overexpresses a different gene product which is essential for proliferation of said organism and wherein the nucleotide sequence of each of the overexpressed genes has been altered so

as to include a nucleotide sequence which can be used to generate a unique product corresponding to each of the overexpressed genes, wherein said culture comprises a strain in which a gene product whose activity or level is inhibited by a nucleic acid comprising a nucleotide sequence selected from the group consisting of SEQ ID NOs.: 1-6213 is

5   overexpressed;

contacting said culture with a sufficient concentration of said compound to inhibit the proliferation of strains of said organism which do not overexpress said gene product on which said compound acts, such that strains which overexpress said gene product on which said compound acts proliferate more rapidly than strains which do not overexpress said

10   gene product on which said compound acts; and

identifying the gene product which is overexpressed in a strain which proliferated more rapidly in said culture by detecting the unique product corresponding to said gene.

457.   A method for identifying the gene product on which a compound which inhibits proliferation of an organism acts comprising:

15   obtaining a culture comprising a plurality of strains wherein each strain overexpresses a different gene product which is essential for proliferation of said organism and wherein the nucleotide sequence of each of the overexpressed genes has been altered so as to include a nucleotide sequence which can be used to generate a unique product corresponding to each of the overexpressed genes, wherein said culture comprises a strain

20   in which a gene product encoded by a nucleic acid comprising a nucleotide sequence selected from the group consisting of SEQ ID NOs.: 6214-42397 is overexpressed;

contacting said culture with a sufficient concentration of said compound to inhibit the proliferation of strains of said organism which do not overexpress said gene product on which said compound acts, such that strains which overexpress said gene product on which

25   said compound acts proliferate more rapidly than strains which do not overexpress said gene product on which said compound acts; and

identifying the gene product which is overexpressed in a strain which proliferated more rapidly in said culture by detecting the unique product corresponding to said gene.

458.   A method for identifying the gene product on which a compound which inhibits

30   proliferation of an organism acts comprising:

obtaining a culture comprising a plurality of strains wherein each strain overexpresses a different gene product which is essential for proliferation of said organism and wherein the nucleotide sequence of each of the overexpressed genes has been altered so as to include a nucleotide sequence which can be used to generate a unique product

35   corresponding to each of the overexpressed genes, wherein said culture comprises a strain in which a gene product comprising an amino acid sequence selected from the group consisting of SEQ ID NOs.: 42938-78581 is overexpressed;

contacting said culture with a sufficient concentration of said compound to inhibit the proliferation of strains of said organism which do not overexpress said gene product on which said compound acts, such that strains which overexpress said gene product on which said compound acts proliferate more rapidly than strains which do not overexpress said

5   gene product on which said compound acts; and

identifying the gene product which is overexpressed in a strain which proliferated more rapidly in said culture by detecting the unique product corresponding to said gene.

459.   A method for identifying the gene product on which a compound which inhibits proliferation of an organism acts comprising:

10   obtaining a culture comprising a plurality of strains wherein each strain overexpresses a different gene product which is essential for proliferation of said organism and wherein the nucleotide sequence of each of the overexpressed genes has been altered so as to include a nucleotide sequence which can be used to generate a unique product corresponding to each of the overexpressed genes, wherein said culture comprises a strain

15   in which a gene product selected from the group consisting of a gene product having at least 70% nucleotide sequence identity as determined using BLASTN version 2.0 with the default parameters to a gene product whose expression is inhibited by an antisense nucleic acid comprising a nucleotide sequence selected from the group consisting of SEQ ID NOs.: 1-6213, a gene product encoded by a nucleic acid having at least 70% nucleotide sequence

20   identity as determined using BLASTN version 2.0 with the default parameters to a nucleic acid encoding a gene product whose expression is inhibited by an antisense nucleic acid comprising a nucleotide sequence selected from the group consisting of SEQ ID NOs: 1-6213, a gene product having at least 25% amino acid identity as determined using FASTA version 3.0t78 with the default parameters to a gene product whose expression is inhibited

25   by an antisense nucleic acid comprising a nucleotide sequence selected from the group consisting of SEQ ID NOs.: 1-6213, a gene product encoded by a nucleic acid which hybridizes to a nucleic acid comprising a nucleotide sequence selected from the group consisting of SEQ ID NOs.: 1-6213 under stringent conditions, a gene product encoded by a nucleic acid which hybridizes to a nucleic acid comprising a nucleotide sequence selected

30   from the group consisting of SEQ ID NOs.: 1-6213 under moderate conditions, and a gene product whose activity may be complemented by the gene product whose activity is inhibited by a nucleic acid comprising a nucleotide sequence selected from the group consisting of SEQ ID NOs: 1-6213 is overexpressed;

contacting said culture with a sufficient concentration of said compound to inhibit

35   the proliferation of strains of said organism which do not overexpress said gene product on which said compound acts, such that strains which overexpress said gene product on which said compound acts proliferate more rapidly than strains which do not overexpress said gene product on which said compound acts; and

identifying the gene product which is overexpressed in a strain which proliferated more rapidly in said culture by detecting the unique product corresponding to said gene.

460.   A method for identifying the gene product on which a compound which inhibits proliferation of an organism acts comprising:

5   obtaining a culture comprising a plurality of strains wherein each strain overexpresses a different gene product which is essential for proliferation of said organism and wherein the nucleotide sequence of each of the overexpressed genes has been altered so as to include a nucleotide sequence which can be used to generate a unique product corresponding to each of the overexpressed genes, wherein said culture comprises a strain

10   in which a gene product encoded by a nucleic acid comprising a nucleotide sequence selected from the group consisting of a nucleic acid comprising a nucleic acid having at least 70% nucleotide sequence identity as determined using BLASTN version 2.0 with the default parameters to a nucleotide sequence selected from the group consisting of SEQ ID NOS.: 6214-42397, a nucleic acid comprising a nucleotide sequence which hybridizes to a

15   sequence selected from the group consisting of SEQ ID NOS.: 6214-42397 under stringent conditions, and a nucleic acid comprising a nucleotide sequence which hybridizes to a nucleotide sequence selected from the group consisting of SEQ ID NOS.: 6214-42397 under moderate conditions is overexpressed;

              contacting said culture with a sufficient concentration of said compound to inhibit

20   the proliferation of strains of said organism which do not overexpress said gene product on which said compound acts, such that strains which overexpress said gene product on which said compound acts proliferate more rapidly than strains which do not overexpress said gene product on which said compound acts; and

              identifying the gene product which is overexpressed in a strain which proliferated

25   more rapidly in said culture by detecting the unique product corresponding to said gene.

461.   A method for identifying the gene product on which a compound which inhibits proliferation of an organism acts comprising:

              obtaining a culture comprising a plurality of strains wherein each strain overexpresses a different gene product which is essential for proliferation of said organism

30   and wherein the nucleotide sequence of each of the overexpressed genes has been altered so as to include a nucleotide sequence which can be used to generate a unique product corresponding to each of the overexpressed genes, wherein said culture comprises a strain in which a gene product comprises a polypeptide selected from the group consisting of a polypeptide having at least 25% amino acid identity as determined using FASTA version

35   3.0t78 to a polypeptide selected from the group consisting of SEQ ID NOs.: 42938-78581 and a polypeptide whose activity may be complemented by a polypeptide selected from the group consisting of SEQ ID NOs: 42938-78581 is overexpressed;

contacting said culture with a sufficient concentration of said compound to inhibit the proliferation of strains of said organism which do not overexpress said gene product on which said compound acts, such that strains which overexpress said gene product on which said compound acts proliferate more rapidly than strains which do not overexpress said

5   gene product on which said compound acts; and

identifying the gene product which is overexpressed in a strain which proliferated more rapidly in said culture by detecting the unique product corresponding to said gene.

462.   The method of Paragraph 456, 457, 458, 459, 460 or 461, wherein the nucleotide sequence of each of the genes encoding an overexpressed gene product has been altered by

10   replacing the native promoters of said genes with promoters which facilitate overexpression of said gene products.

463.   The method of Paragraph 456, 457, 458, 459, 460 or 461, wherein the nucleotide sequence of each of the genes encoding an overexpressed gene product has been altered by inserting a regulatory element into the native promoters of said genes with a promoter which facilitates

15   overexpression of said gene products.

464.   The method of Paragraph 463, wherein said regulatory element is selected from the group consisting of a regulatable promoter, an operator which is recognized by a repressor, a nucleotide sequence which is recognized by a transcriptional activator, a transcriptional terminator, a nucleotide sequence which introduces a bend in the DNA and an upstream activating sequence.

20   465.   The method of Paragraph 456, 457, 458, 459, 460 or 461, wherein the step of identifying the gene product which is overexpressed in a strain which proliferated more rapidly in said culture by detecting the unique product corresponding to said gene comprises performing an amplification reaction and detecting a unique amplification product corresponding to said gene.

466.   The method of Paragraph 462, wherein the native promoter of each of the genes

25   encoding a gene product essential for proliferation is replaced with the same promoter.

467.   The method of Paragraph 462, wherein the native promoters of the genes encoding gene products essential for proliferation are replaced with a plurality of promoters selected to give a desired expression level for each gene product.

468.   The method of Paragraph 462, wherein said promoters which replaced the native

30   promoters in each strain comprise regulatable promoters.

469.   The method of Paragraph 462, wherein said promoters which replaced the native promoters in each strain each strain comprise constitutive promoters.

470.   The method of Paragraph 456, 457, 458, 459, 460 or 461, wherein said organism is selected from the group consisting of bacteria, fungi, and protozoa.

35   471.   The method of Paragraph 456, 457, 458, 459, 460 or 461, wherein said culture is a culture of an organism selected from the group consisting of *Acinetobacter baumannii, Anaplasma marginale, Aspergillus fumigatus, Bacillus anthracis, Bacteroides fragilis, Bordetella pertussis, Borrelia burgdorferi, Burkholderia cepacia, Burkholderia fungorum, Burkholderia mallei,*

Campylobacter jejuni, Candida albicans, Candida glabrata (also called *Torulopsis glabrata*), *Candida tropicalis, Candida parapsilosis, Candida guilliermondii, Candida krusei, Candida kefyr* (also called *Candida pseudotropicalis*), *Candida dubliniensis, Chlamydia pneumoniae, Chlamydia trachomatis, Clostridium acetobutylicum, Clostridium botulinum, Clostridium difficile, Clostridium* perfringens, *Coccidioides immitis, Corynebacterium diptheriae, Cryptococcus neoformans, Enterobacter cloacae, Enterococcus faecalis, Enterococcus faecium, Escherichia coli, Haemophilus influenzae, Helicobacter pylori, Histoplasma capsulatum, Klebsiella pneumoniae, Legionella pneumophila, Listeria monocytogenes, Moraxella catarrhalis, Mycobacterium avium, Mycobacterium bovis, Mycobacterium leprae, Mycobacterium tuberculosis, Mycoplasma* genitalium, *Mycoplasma pneumoniae, Neisseria gonorrhoeae, Neisseria meningitidis, Nocardia asteroides, Pasteurella haemolytica, Pasteurella multocida, Pneumocystis carinii, Proteus mirabilis, Proteus vulgaris, Pseudomonas aeruginosa, Pseudomonas putida, Pseudomonas syringae, Salmonella bongori, Salmonella cholerasuis, Salmonella enterica, Salmonella paratyphi, Salmonella typhi, Salmonella typhimurium, Shigella boydii, Shigella dysenteriae, Shigella flexneri,* Shigella sonnei, *Staphylococcus aureus, Staphylococcus epidermidis, Staphylococcus haemolyticus, Streptococcus pneumoniae, Streptococcus mutans, Streptococcus pyogenes, Treponema pallidum, Ureaplasma urealyticum, Vibrio cholerae, Vibrio parahaemolyticus, Vibrio vulnificans, Yersinia enterocolitica, Yersinia pestis* and any species falling within the genera of any of the above species.

472.   A method for identifying the gene product on which a compound which inhibits proliferation of an organism acts comprising:

obtaining a culture comprising a plurality of strains wherein each strain underexpresses a different gene product which is essential for proliferation of said organism and wherein the nucleotide sequence of each of the underexpressed genes has been altered so as to include a nucleotide sequence which can be used to generate a unique product corresponding to each of the underexpressed genes and wherein said culture comprises a strain in which a gene product whose activity or level is inhibited by a nucleic acid comprising a nucleotide sequence selected from the group consisting of SEQ ID NOs.: 1-6213 is underexpressed;

contacting said culture with a sufficient concentration of said compound to inhibit the proliferation of strains of said organism which underexpress said gene product on which said compound acts, such that strains which underexpress said gene product on which said compound acts proliferate more slowly than strains which do not underexpress the gene product on which said compound acts; and

identifying the gene product which is underexpressed in a strain which proliferated more rapidly in said culture by detecting the unique product corresponding to said gene.

473.   A method for identifying the gene product on which a compound which inhibits proliferation of an organism acts comprising:

obtaining a culture comprising a plurality of strains wherein each strain underexpresses a different gene product which is essential for proliferation of said organism and wherein the nucleotide sequence of each of the underexpressed genes has been altered so as to include a nucleotide sequence which can be used to generate a unique product

5   corresponding to each of the underexpressed genes and wherein said culture comprises a strain in which a gene product encoded by a nucleic acid comprising a nucleotide sequence selected from the group consisting of SEQ ID NOs.: 6214-42397 is underexpressed;

contacting said culture with a sufficient concentration of said compound to inhibit the proliferation of strains of said organism which underexpress said gene product on which

10   said compound acts, such that strains which underexpress said gene product on which said compound acts proliferate more slowly than strains which do not underexpress the gene product on which said compound acts; and

identifying the gene product which is underexpressed in a strain which proliferated more rapidly in said culture by detecting the unique product corresponding to said gene.

15   474.   A method for identifying the gene product on which a compound which inhibits proliferation of an organism acts comprising:

obtaining a culture comprising a plurality of strains wherein each strain underexpresses a different gene product which is essential for proliferation of said organism and wherein the nucleotide sequence of each of the underexpressed genes has been altered

20   so as to include a nucleotide sequence which can be used to generate a unique product corresponding to each of the underexpressed genes, wherein said culture comprises a strain in which a gene product comprising an amino acid sequence selected from the group consisting of SEQ ID NOs.: 42938-78581 is underexpressed;

contacting said culture with a sufficient concentration of said compound to inhibit

25   the proliferation of strains of said organism which underexpress said gene product on which said compound acts, such that strains which underexpress said gene product on which said compound acts proliferate more slowly than strains which do not underexpress the gene product on which said compound acts; and

identifying the gene product which is underexpressed in a strain which proliferated

30   more rapidly in said culture by detecting the unique product corresponding to said gene.

475.   A method for identifying the gene product on which a compound which inhibits proliferation of an organism acts comprising:

obtaining a culture comprising a plurality of strains wherein each strain underexpresses a different gene product which is essential for proliferation of said organism

35   and wherein the nucleotide sequence of each of the underexpressed genes has been altered so as to include a nucleotide sequence which can be used to generate a unique product corresponding to each of the underexpressed genes, wherein said culture comprises a strain in which a gene product selected from the group consisting of a gene product having at

least 70% nucleotide sequence identity as determined using BLASTN version 2.0 with the
default parameters to a gene product whose expression is inhibited by an antisense nucleic
acid comprising a nucleotide sequence selected from the group consisting of SEQ ID NOs.:
1-6213, a gene product encoded by a nucleic acid having at least 70% nucleotide sequence

5   identity as determined using BLASTN version 2.0 with the default parameters to a nucleic
acid encoding a gene product whose expression is inhibited by an antisense nucleic acid
comprising a nucleotide sequence selected from the group consisting of SEQ ID NOs: 1-
6213, a gene product having at least 25% amino acid identity as determined using FASTA
version 3.0t78 with the default parameters to a gene product whose expression is inhibited

10   by an antisense nucleic acid comprising a nucleotide sequence selected from the group
consisting of SEQ ID NOs.: 1-6213, a gene product encoded by a nucleic acid which
hybridizes to a nucleic acid comprising a nucleotide sequence selected from the group
consisting of SEQ ID NOs.: 1-6213 under stringent conditions, a gene product encoded by
a nucleic acid which hybridizes to a nucleic acid comprising a nucleotide sequence selected

15   from the group consisting of SEQ ID NOs.: 1-6213 under moderate conditions, and a gene
product whose activity may be complemented by the gene product whose activity is
inhibited by a nucleic acid comprising a nucleotide sequence selected from the group
consisting of SEQ ID NOs: 1-6213 is underexpressed;

contacting said culture with a sufficient concentration of said compound to inhibit

20   the proliferation of strains of said organism which underexpress said gene product on which
said compound acts, such that strains which underexpress said gene product on which said
compound acts proliferate more slowly than strains which do not underexpress the gene
product on which said compound acts; and

identifying the gene product which is underexpressed in a strain which proliferated

25   more rapidly in said culture by detecting the unique product corresponding to said gene.

476.   A method for identifying the gene product on which a compound which inhibits
proliferation of an organism acts comprising:

obtaining a culture comprising a plurality of strains wherein each strain
underexpresses a different gene product which is essential for proliferation of said organism

30   and wherein the nucleotide sequence of each of the underexpressed genes has been altered
so as to include a nucleotide sequence which can be used to generate a unique product
corresponding to each of the underexpressed genes, wherein said culture comprises a strain
in which a gene product encoded by a nucleic acid comprising a nucleotide sequence
selected from the group consisting of a nucleic acid comprising a nucleic acid having at

35   least 70% nucleotide sequence identity as determined using BLASTN version 2.0 with the
default parameters to a nucleotide sequence selected from the group consisting of SEQ ID
NOS.: 6214-42397, a nucleic acid comprising a nucleotide sequence which hybridizes to a
sequence selected from the group consisting of SEQ ID NOS.: 6214-42397 under stringent

conditions, and a nucleic acid comprising a nucleotide sequence which hybridizes to a nucleotide sequence selected from the group consisting of SEQ ID NOS.: 6214-42397 under moderate conditions is underexpressed;

contacting said culture with a sufficient concentration of said compound to inhibit the proliferation of strains of said organism which underexpress said gene product on which said compound acts, such that strains which underexpress said gene product on which said compound acts proliferate more slowly than strains which do not underexpress the gene product on which said compound acts; and

identifying the gene product which is underexpressed in a strain which proliferated more rapidly in said culture by detecting the unique product corresponding to said gene.

477.   A method for identifying the gene product on which a compound which inhibits proliferation of an organism acts comprising:

obtaining a culture comprising a plurality of strains wherein each strain underexpresses a different gene product which is essential for proliferation of said organism and wherein the nucleotide sequence of each of the underexpressed genes has been altered so as to include a nucleotide sequence which can be used to generate a unique product corresponding to each of the underexpressed genes , wherein said culture comprises a strain in which a gene product comprises a polypeptide selected from the group consisting of a polypeptide having at least 25% amino acid identity as determined using FASTA version 3.0t78 to a polypeptide selected from the group consisting of SEQ ID NOs.: 42938-78581 and a polypeptide whose activity may be complemented by a polypeptide selected from the group consisting of SEQ ID NOs: 42938-78581 is underexpressed;

contacting said culture with a sufficient concentration of said compound to inhibit the proliferation of strains of said organism which underexpress said gene product on which said compound acts, such that strains which underexpress said gene product on which said compound acts proliferate more slowly than strains which do not underexpress the gene product on which said compound acts; and

identifying the gene product which is underexpressed in a strain which proliferated more rapidly in said culture by detecting the unique product corresponding to said gene.

478.   The method of Paragraph 472, 473, 474, 475, 476 or 477, wherein the nucleotide sequence of each of the genes encoding an underexpressed gene product has been altered by replacing the native promoters of said genes with promoters which facilitate underexpression of said gene products.

479.   The method of Paragraph 472, 473, 474, 475, 476 or 477, wherein the nucleotide sequence of each of the genes encoding an underexpressed gene product has been altered by inserting a regulatory element into the native promoters of said genes with a promoter which facilitates underexpression of said gene products.

480.   The method of Paragraph 479, wherein said regulatory element is selected from the group consisting of a regulatable promoter, an operator which is recognized by a repressor, a nucleotide sequence which is recognized by a transcriptional activator, a transcriptional terminator, a nucleotide sequence which introduces a bend in the DNA and an upstream activating sequence.

481.   The method of Paragraph 472, 473, 474, 475, 476 or 477, wherein the step of identifying the gene product which is underexpressed in a strain which proliferated more slowly in said culture by detecting the unique product corresponding to said gene comprises performing an amplification reaction and detecting a unique amplification product corresponding to said gene.

482.   The method of Paragraph 478, wherein the native promoter of each of the genes encoding a gene product essential for proliferation is replaced with the same promoter.

483.   The method of Paragraph 478, wherein the native promoters of the genes encoding gene products essential for proliferation are replaced with a plurality of promoters selected to give a desired expression level for each gene product.

484.   The method of Paragraph 478, wherein said promoters which replaced the native promoters in each strain comprise regulatable promoters.

485.   The method of Paragraph 478, wherein said promoters which replaced the native promoters in each strain each strain comprise constitutive promoters.

486.   The method of Paragraph 472, 473, 474, 475, 476 or 477, wherein said organism is selected from the group consisting of bacteria, fungi, and protozoa.

487.   The method of Paragraph 472, 473, 474, 475, 476 or 477, wherein said culture is a culture of an organism selected from the group consisting of *Acinetobacter baumannii, Anaplasma marginale, Aspergillus fumigatus, Bacillus anthracis, Bacteroides fragilis, Bordetella pertussis, Borrelia burgdorferi, Burkholderia cepacia, Burkholderia fungorum, Burkholderia mallei, Campylobacter jejuni, Candida albicans, Candida glabrata* (also called *Torulopsis glabrata*), *Candida tropicalis, Candida parapsilosis, Candida guilliermondii, Candida krusei, Candida kefyr* (also called *Candida pseudotropicalis*), *Candida dubliniensis, Chlamydia pneumoniae, Chlamydia trachomatis, Clostridium acetobutylicum, Clostridium botulinum, Clostridium difficile, Clostridium perfringens, Coccidioides immitis, Corynebacterium diptheriae, Cryptococcus neoformans, Enterobacter cloacae, Enterococcus faecalis, Enterococcus faecium, Escherichia coli, Haemophilus influenzae, Helicobacter pylori, Histoplasma capsulatum, Klebsiella pneumoniae, Legionella pneumophila, Listeria monocytogenes, Moraxella catarrhalis, Mycobacterium avium, Mycobacterium bovis, Mycobacterium leprae, Mycobacterium tuberculosis, Mycoplasma genitalium, Mycoplasma pneumoniae, Neisseria gonorrhoeae, Neisseria meningitidis, Nocardia asteroides, Pasteurella haemolytica, Pasteurella multocida, Pneumocystis carinii, Proteus mirabilis, Proteus vulgaris, Pseudomonas aeruginosa, Pseudomonas putida, Pseudomonas syringae, Salmonella bongori, Salmonella cholerasuis, Salmonella enterica, Salmonella paratyphi, Salmonella typhi, Salmonella typhimurium, Shigella boydii, Shigella dysenteriae, Shigella flexneri, Shigella sonnei, Staphylococcus aureus, Staphylococcus epidermidis, Staphylococcus haemolyticus,*

Streptococcus pneumoniae, Streptococcus mutans, Streptococcus pyogenes, Treponema pallidum, Ureaplasma urealyticum, Vibrio cholerae, Vibrio parahaemolyticus, Vibrio vulnificans, Yersinia enterocolitica, Yersinia pestis and any species falling within the genera of any of the above species.

488.   A method for determining the extent to which each of a plurality of strains are present in a culture or collection of strains comprising:

obtaining a nucleic acid sample comprising nucleic acids from a culture or collection of strains wherein said culture or collection of strains comprises a plurality of strains wherein each strain overexpresses or underexpresses a different gene product which is required for proliferation of said organism wherein said culture comprises a strain in which a gene product whose activity or level is inhibited by a nucleic acid comprising a nucleotide sequence selected from the group consisting of SEQ ID NOs.: 1-6213 is overexpressed or underexpressed;

performing an amplification reaction using a set of primer pairs which are complementary to nucleotide sequences within or adjacent to the genes which encode said gene products, wherein the members of said set of primer pairs are designed such that each primer pair would yield an amplification product having a length distinguishable from the lengths of the amplification products from the other primer pairs if a strain comprising the nucleotide sequences complementary to said primer pair is present in said culture or collection of strains; and

determining the lengths of the amplification products obtained in said amplification reaction.

489.   A method for determining the extent to which each of a plurality of strains are present in a culture or collection of strains comprising:

obtaining a nucleic acid sample comprising nucleic acids from a culture or collection of strains wherein said culture or collection of strains comprises a plurality of strains wherein each strain overexpresses or underexpresses a different gene product which is required for proliferation of said organism , wherein said culture comprises a strain in which a gene product encoded by a nucleic acid comprising a nucleotide sequence selected from the group consisting of SEQ ID NOs.: 6214-42397 is overexpressed or underexpressed;

performing an amplification reaction using a set of primer pairs which are complementary to nucleotide sequences within or adjacent to the genes which encode said gene products, wherein the members of said set of primer pairs are designed such that each primer pair would yield an amplification product having a length distinguishable from the lengths of the amplification products from the other primer pairs if a strain comprising the nucleotide sequences complementary to said primer pair is present in said culture or collection of strains; and

determining the lengths of the amplification products obtained in said amplification

reaction.

490.   A method for determining the extent to which each of a plurality of strains are

present in a culture or collection of strains comprising:

5   obtaining a nucleic acid sample comprising nucleic acids from a culture or

collection of strains wherein said culture or collection of strains comprises a plurality of

strains wherein each strain overexpresses or underexpresses a different gene product which

is required for proliferation of said organism, wherein said culture comprises a strain in

which a gene product comprising an amino acid sequence selected from the group

10   consisting of SEQ ID NOs.: 42938-78581 is overexpressed or underexpressed;

performing an amplification reaction using a set of primer pairs which are

complementary to nucleotide sequences within or adjacent to the genes which encode said

gene products, wherein the members of said set of primer pairs are designed such that each

primer pair would yield an amplification product having a length distinguishable from the

15   lengths of the amplification products from the other primer pairs if a strain comprising the

nucleotide sequences complementary to said primer pair is present in said culture or

collection of strains; and

determining the lengths of the amplification products obtained in said amplification

reaction.

20   491.   A method for determining the extent to which each of a plurality of strains are

present in a culture or collection of strains comprising:

obtaining a nucleic acid sample comprising nucleic acids from a culture or

collection of strains wherein said culture or collection of strains comprises a plurality of

strains wherein each strain overexpresses or underexpresses a different gene product which

25   is required for proliferation of said organism , wherein said culture comprises a strain in

which a gene product selected from the group consisting of a gene product having at least

70% nucleotide sequence identity as determined using BLASTN version 2.0 with the

default parameters to a gene product whose expression is inhibited by an antisense nucleic

acid comprising a nucleotide sequence selected from the group consisting of SEQ ID NOs.:

30   1-6213, a gene product encoded by a nucleic acid having at least 70% nucleotide sequence

identity as determined using BLASTN version 2.0 with the default parameters to a nucleic

acid encoding a gene product whose expression is inhibited by an antisense nucleic acid

comprising a nucleotide sequence selected from the group consisting of SEQ ID NOs: 1-

6213, a gene product having at least 25% amino acid identity as determined using FASTA

35   version 3.0t78 with the default parameters to a gene product whose expression is inhibited

by an antisense nucleic acid comprising a nucleotide sequence selected from the group

consisting of SEQ ID NOs.: 1-6213, a gene product encoded by a nucleic acid which

hybridizes to a nucleic acid comprising a nucleotide sequence selected from the group

consisting of SEQ ID NOs.: 1-6213 under stringent conditions, a gene product encoded by
a nucleic acid which hybridizes to a nucleic acid comprising a nucleotide sequence selected
from the group consisting of SEQ ID NOs.: 1-6213 under moderate conditions, and a gene
product whose activity may be complemented by the gene product whose activity is

5   inhibited by a nucleic acid comprising a nucleotide sequence selected from the group
consisting of SEQ ID NOs: 1-6213 is overexpressed or underexpressed;

performing an amplification reaction using a set of primer pairs which are
complementary to nucleotide sequences within or adjacent to the genes which encode said
gene products, wherein the members of said set of primer pairs are designed such that each

10   primer pair would yield an amplification product having a length distinguishable from the
lengths of the amplification products from the other primer pairs if a strain comprising the
nucleotide sequences complementary to said primer pair is present in said culture or
collection of strains; and

determining the lengths of the amplification products obtained in said amplification

15   reaction.

492.   A method for determining the extent to which each of a plurality of strains are
present in a culture or collection of strains comprising:

obtaining a nucleic acid sample comprising nucleic acids from a culture or
collection of strains wherein said culture or collection of strains comprises a plurality of

20   strains wherein each strain overexpresses or underexpresses a different gene product which
is required for proliferation of said organism , wherein said culture comprises a strain in
which a gene product encoded by a nucleic acid comprising a nucleotide sequence selected
from the group consisting of a nucleic acid comprising a nucleic acid having at least 70%
nucleotide sequence identity as determined using BLASTN version 2.0 with the default

25   parameters to a nucleotide sequence selected from the group consisting of SEQ ID NOS.:
6214-42397, a nucleic acid comprising a nucleotide sequence which hybridizes to a
sequence selected from the group consisting of SEQ ID NOS.: 6214-42397 under stringent
conditions, and a nucleic acid comprising a nucleotide sequence which hybridizes to a
nucleotide sequence selected from the group consisting of SEQ ID NOS.: 6214-42397

30   . under moderate conditions is overexpressed or underexpressed;

performing an amplification reaction using a set of primer pairs which are
complementary to nucleotide sequences within or adjacent to the genes which encode said
gene products, wherein the members of said set of primer pairs are designed such that each
primer pair would yield an amplification product having a length distinguishable from the

35   lengths of the amplification products from the other primer pairs if a strain comprising the
nucleotide sequences complementary to said primer pair is present in said culture or
collection of strains; and

determining the lengths of the amplification products obtained in said amplification reaction.

493.   A method for determining the extent to which each of a plurality of strains are present in a culture or collection of strains comprising:

5   obtaining a nucleic acid sample comprising nucleic acids from a culture or collection of strains wherein said culture or collection of strains comprises a plurality of strains wherein each strain overexpresses or underexpresses a different gene product which is required for proliferation of said organism , wherein said culture comprises a strain in which a gene product comprising a polypeptide selected from the group consisting of a

10   polypeptide having at least 25% amino acid identity as determined using FASTA version 3.0t78 to a polypeptide selected from the group consisting of SEQ ID NOs.: 42938-78581 and a polypeptide whose activity may be complemented by a polypeptide selected from the group consisting of SEQ ID NOs: 42938-78581 is overexpressed or underexpressed;

            performing an amplification reaction using a set of primer pairs which are

15   complementary to nucleotide sequences within or adjacent to the genes which encode said gene products, wherein the members of said set of primer pairs are designed such that each primer pair would yield an amplification product having a length distinguishable from the lengths of the amplification products from the other primer pairs if a strain comprising the nucleotide sequences complementary to said primer pair is present in said culture or

20   collection of strains; and

            determining the lengths of the amplification products obtained in said amplification reaction.

494.   The method of Paragraph 488, 489, 490, 491, 492 or 493, wherein one member of each primer pair for each of said genes is labeled with a detectable dye.

25   495.   The method of Paragraph 488, 489, 490, 491, 492 or 493, wherein:

            said nucleic acid sample is divided into N aliquots; and

            said amplification reaction is performed on each aliquot using primer pairs complementary to nucleotide sequences within or adjacent to 1/N of the genes which encode said gene products, wherein one of the members of each primer pair in each aliquot

30   is labeled with a dye and wherein the dyes on the primers in each aliquot are distinguishable from one another.

496.   The method of Paragraph 494, further comprising pooling the amplification products from each of the aliquots prior to determining the lengths of the amplification products.

497.   The method of Paragraph 488, 489, 490, 491, 492 or 493, wherein the native

35   promoters of said genes which encode said gene products have been replaced with a regulatable promoter and one of the primers in said primer pairs is complementary to a nucleotide sequence within said regulatable promoter.

498.   The method of Paragraph 496, wherein the native promoters for each of said genes were replaced with the same regulatable promoter.

499.   The method of Paragraph 496, wherein more than one regulatable promoter was used to replace the promoters of said genes such that some of said genes are under the control of a different regulatable promoter.

500.   A method for identifying the target of a compound which inhibits the proliferation of an organism comprising:

obtaining a first nucleic acid sample comprising nucleic acids from a first culture or collection of strains wherein said culture or collection of strains comprises a plurality of strains wherein each strain overexpresses or underexpresses a different gene product which is required for proliferation of said organism and wherein said culture or collection of strains has been contacted with said compound;

obtaining a second nucleic acid sample comprising nucleic acids from a second culture or collection of strains wherein said culture or collection of strains comprises the same strains as said first culture or collection of strains wherein said second culture or collection of strains has not been contacted with said compound;

performing a first amplification reaction on said first nucleic acid sample using a set of primer pairs which are complementary to nucleotide sequences within or adjacent to the genes which encode said gene products, wherein the members of said set of primer pairs are designed such that each primer pair would yield an amplification product having a length distinguishable from the lengths of the amplification products from the other primer pairs if a strain comprising the nucleotide sequences complementary to said primer pair is present in said culture or collection of strains;

performing a second amplification reaction on said second nucleic acid sample using the same set of primer pairs used in said first amplification reaction;

and comparing the amount of each amplification product in said first amplification reaction to the amount of that amplification product in said second amplification reaction, wherein an increased level of an amplification product in said first amplification reaction relative to said second amplification reaction indicates that the gene product corresponding to said amplification product is the target of said compound if said culture or strain overexpresses said gene products and a decreased level of of an amplification product in said first amplification reaction relative to said second amplification reaction indicates that the gene product corresponding to said amplification product is the target of said compound if said culture or strain overexpresses said gene products, wherein said first and second cultures or collection of strains comprise a strain in which a gene product whose activity or level is inhibited by a nucleic acid comprising a nucleotide sequence selected from the group consisting of SEQ ID NOs.: 1-6213 is overexpressed or underexpressed.

501.   A method for identifying the target of a compound which inhibits the proliferation of an organism comprising:

obtaining a first nucleic acid sample comprising nucleic acids from a first culture or collection of strains wherein said culture or collection of strains comprises a plurality of strains wherein each strain overexpresses or underexpresses a different gene product which is required for proliferation of said organism and wherein said culture or collection of strains has been contacted with said compound;

obtaining a second nucleic acid sample comprising nucleic acids from a second culture or collection of strains wherein said culture or collection of strains comprises the same strains as said first culture or collection of strains wherein said second culture or collection of strains.has not been contacted with said compound;

performing a first amplification reaction on said first nucleic acid sample using a set of primer pairs which are complementary to nucleotide sequences within or adjacent to the genes which encode said gene products, wherein the members of said set of primer pairs are designed such that each primer pair would yield an amplification product having a length distinguishable from the lengths of the amplification products from the other primer pairs if a strain comprising the nucleotide sequences complementary to said primer pair is present in said culture or collection of strains;

performing a second amplification reaction on said second nucleic acid sample using the same set of primer pairs used in said first amplification reaction;

and comparing the amount of each amplification product in said first amplification reaction to the amount of that amplification product in said second amplification reaction, wherein an increased level of an amplification product in said first amplification reaction relative to said second amplification reaction indicates that the gene product corresponding to said amplification product is the target of said compound if said culture or strain overexpresses said gene products and a decreased level of of an amplification product in said first amplification reaction relative to said second amplification reaction indicates that the gene product corresponding to said amplification product is the target of said compound if said culture or strain overexpresses said gene products, wherein said first and second cultures or collection of strains comprise a strain in which a gene product encoded by a nucleic acid comprising a nucleotide sequence selected from the group consisting of SEQ ID NOs.: 6214-42397 is overexpressed or underexpressed.

502.   A method for identifying the target of a compound which inhibits the proliferation of an organism comprising:

obtaining a first nucleic acid sample comprising nucleic acids from a first culture or collection of strains wherein said culture or collection of strains comprises a plurality of strains wherein each strain overexpresses or underexpresses a different gene product which

is required for proliferation of said organism and wherein said culture or collection of strains has been contacted with said compound;

obtaining a second nucleic acid sample comprising nucleic acids from a second culture or collection of strains wherein said culture or collection of strains comprises the same strains as said first culture or collection of strains wherein said second culture or collection of strains has not been contacted with said compound;

performing a first amplification reaction on said first nucleic acid sample using a set of primer pairs which are complementary to nucleotide sequences within or adjacent to the genes which encode said gene products, wherein the members of said set of primer pairs are designed such that each primer pair would yield an amplification product having a length distinguishable from the lengths of the amplification products from the other primer pairs if a strain comprising the nucleotide sequences complementary to said primer pair is present in said culture or collection of strains;

performing a second amplification reaction on said second nucleic acid sample using the same set of primer pairs used in said first amplification reaction;

and comparing the amount of each amplification product in said first amplification reaction to the amount of that amplification product in said second amplification reaction, wherein an increased level of an amplification product in said first amplification reaction relative to said second amplification reaction indicates that the gene product corresponding to said amplification product is the target of said compound if said culture or strain overexpresses said gene products and a decreased level of of an amplification product in said first amplification reaction relative to said second amplification reaction indicates that the gene product corresponding to said amplification product is the target of said compound if said culture or strain overexpresses said gene products, wherein said first and second cultures or collection of strains comprise a strain in which a gene product comprising an amino acid sequence selected from the group consisting of SEQ ID NOs.: 42938-78581 is overexpressed or underexpressed.

503.   A method for identifying the target of a compound which inhibits the proliferation of an organism comprising:

obtaining a first nucleic acid sample comprising nucleic acids from a first culture or collection of strains wherein said culture or collection of strains comprises a plurality of strains wherein each strain overexpresses or underexpresses a different gene product which is required for proliferation of said organism and wherein said culture or collection of strains has been contacted with said compound;

obtaining a second nucleic acid sample comprising nucleic acids from a second culture or collection of strains wherein said culture or collection of strains comprises the same strains as said first culture or collection of strains wherein said second culture or collection of strains has not been contacted with said compound;

performing a first amplification reaction on said first nucleic acid sample using a
set of primer pairs which are complementary to nucleotide sequences within or adjacent to
the genes which encode said gene products, wherein the members of said set of primer pairs
are designed such that each primer pair would yield an amplification product having a
length distinguishable from the lengths of the amplification products from the other primer
pairs if a strain comprising the nucleotide sequences complementary to said primer pair is
present in said culture or collection of strains;

performing a second amplification reaction on said second nucleic acid sample
using the same set of primer pairs used in said first amplification reaction;

and comparing the amount of each amplification product in said first amplification
reaction to the amount of that amplification product in said second amplification reaction,
wherein an increased level of an amplification product in said first amplification reaction
relative to said second amplification reaction indicates that the gene product corresponding
to said amplification product is the target of said compound if said culture or strain
overexpresses said gene products and a decreased level of of an amplification product in
said first amplification reaction relative to said second amplification reaction indicates that
the gene product corresponding to said amplification product is the target of said compound
if said culture or strain overexpresses said gene products, wherein said first and second
cultures or collection of strains comprise a strain in which a gene product selected from the
group consisting of a gene product having at least 70% nucleotide sequence identity as
determined using BLASTN version 2.0 with the default parameters to a gene product
whose expression is inhibited by an antisense nucleic acid comprising a nucleotide
sequence selected from the group consisting of SEQ ID NOs.: 1-6213, a gene product
encoded by a nucleic acid having at least 70% nucleotide sequence identity as determined
using BLASTN version 2.0 with the default parameters to a nucleic acid encoding a gene
product whose expression is inhibited by an antisense nucleic acid comprising a nucleotide
sequence selected from the group consisting of SEQ ID NOs: 1-6213, a gene product
having at least 25% amino acid identity as determined using FASTA version 3.0t78 with
the default parameters to a gene product whose expression is inhibited by an antisense
nucleic acid comprising a nucleotide sequence selected from the group consisting of SEQ
ID NOs.: 1-6213, a gene product encoded by a nucleic acid which hybridizes to a nucleic
acid comprising a nucleotide sequence selected from the group consisting of SEQ ID NOs.:
1-6213 under stringent conditions, a gene product encoded by a nucleic acid which
hybridizes to a nucleic acid comprising a nucleotide sequence selected from the group
consisting of SEQ ID NOs.: 1-6213 under moderate conditions, and a gene product whose
activity may be complemented by the gene product whose activity is inhibited by a nucleic
acid comprising a nucleotide sequence selected from the group consisting of SEQ ID NOs:
1-6213 is overexpressed or underexpressed.

504.   A method for identifying the target of a compound which inhibits the proliferation
of an organism comprising:

obtaining a first nucleic acid sample comprising nucleic acids from a first culture or
collection of strains wherein said culture or collection of strains comprises a plurality of
strains wherein each strain overexpresses or underexpresses a different gene product which
is required for proliferation of said organism and wherein said culture or collection of
strains has been contacted with said compound;

obtaining a second nucleic acid sample comprising nucleic acids from a second
culture or collection of strains wherein said culture or collection of strains comprises the
same strains as said first culture or collection of strains wherein said second culture or
collection of strains has not been contacted with said compound;

performing a first amplification reaction on said first nucleic acid sample using a
set of primer pairs which are complementary to nucleotide sequences within or adjacent to
the genes which encode said gene products, wherein the members of said set of primer pairs
are designed such that each primer pair would yield an amplification product having a
length distinguishable from the lengths of the amplification products from the other primer
pairs if a strain comprising the nucleotide sequences complementary to said primer pair is
present in said culture or collection of strains;

performing a second amplification reaction on said second nucleic acid sample
using the same set of primer pairs used in said first amplification reaction;

and comparing the amount of each amplification product in said first amplification
reaction to the amount of that amplification product in said second amplification reaction,
wherein an increased level of an amplification product in said first amplification reaction
relative to said second amplification reaction indicates that the gene product corresponding
to said amplification product is the target of said compound if said culture or strain
overexpresses said gene products and a decreased level of of an amplification product in
said first amplification reaction relative to said second amplification reaction indicates that
the gene product corresponding to said amplification product is the target of said compound
if said culture or strain overexpresses said gene products, wherein said first and second
cultures or collection of strains comprise a strain in which a gene product encoded by a
nucleic acid comprising a nucleotide sequence selected from the group consisting of a
nucleic acid comprising a nucleic acid having at least 70% nucleotide sequence identity as
determined using BLASTN version 2.0 with the default parameters to a nucleotide
sequence selected from the group consisting of SEQ ID NOS.: 6214-42397, a nucleic acid
comprising a nucleotide sequence which hybridizes to a sequence selected from the group
consisting of SEQ ID NOS.: 6214-42397 under stringent conditions, and a nucleic acid
comprising a nucleotide sequence which hybridizes to a nucleotide sequence selected from

the group consisting of SEQ ID NOS.: 6214-42397 under moderate conditions is overexpressed or underexpressed.

505.   A method for identifying the target of a compound which inhibits the proliferation of an organism comprising:

5   obtaining a first nucleic acid sample comprising nucleic acids from a first culture or collection of strains wherein said culture or collection of strains comprises a plurality of strains wherein each strain overexpresses or underexpresses a different gene product which is required for proliferation of said organism and wherein said culture or collection of strains has been contacted with said compound;

10   obtaining a second nucleic acid sample comprising nucleic acids from a second culture or collection of strains wherein said culture or collection of strains comprises the same strains as said first culture or collection of strains wherein said second culture or collection of strains has not been contacted with said compound;

          performing a first amplification reaction on said first nucleic acid sample using a

15   set of primer pairs which are complementary to nucleotide sequences within or adjacent to the genes which encode said gene products, wherein the members of said set of primer pairs are designed such that each primer pair would yield an amplification product having a length distinguishable from the lengths of the amplification products from the other primer pairs if a strain comprising the nucleotide sequences complementary to said primer pair is

20   present in said culture or collection of strains;

          performing a second amplification reaction on said second nucleic acid sample using the same set of primer pairs used in said first amplification reaction;

          and comparing the amount of each amplification product in said first amplification reaction to the amount of that amplification product in said second amplification reaction,

25   wherein an increased level of an amplification product in said first amplification reaction relative to said second amplification reaction indicates that the gene product corresponding to said amplification product is the target of said compound if said culture or strain overexpresses said gene products and a decreased level of of an amplification product in said first amplification reaction relative to said second amplification reaction indicates that

30   the gene product corresponding to said amplification product is the target of said compound if said culture or strain overexpresses said gene products, wherein said first and second culture or collection of strains comprise a strain in which a gene product comprising a polypeptide selected from the group consisting of a polypeptide having at least 25% amino acid identity as determined using FASTA version 3.0t78 to a polypeptide selected from the

35   group consisting of SEQ ID NOs.: 42938-78581 and a polypeptide whose activity may be complemented by a polypeptide selected from the group consisting of SEQ ID NOs: 42938-78581 is overexpressed or underexpressed.

506.   The method of Paragraph 500, 501, 502, 503, 504 or 505, wherein one member of each primer pair for each of said genes is labeled with a detectable dye.

507.   The method of Paragraph 500, 501, 502, 503, 504 or 505, wherein the native promoters of said genes which encode said gene products have been replaced with a regulatable promoter and one of the primers in said primer pairs is complementary to a nucleotide sequence within said regulatable promoter.

508.   The method of Paragraph 500, 501, 502, 503, 504 or 505, wherein the native promoters for each of said genes were replaced with the same regulatable promoter.

509.   The method of Paragraph 500, 501, 502, 503, 504 or 505, wherein more than one regulatable promoter was used to replace the promoters of said genes such that some of said genes are under the control of a different regulatable promoter.

510.   A method for determining the extent to which each of a plurality of strains are present in a culture or collection of strains comprising:

obtaining a nucleic acid sample comprising nucleic acids from a culture or collection of strains wherein said culture or collection of strains comprises a plurality of strains which transcribe an antisense nucleic acid complementary to a different gene product which is required for proliferation of said organism;

performing an amplification reaction using a set of primer pairs which are complementary to nucleotide sequences within or adjacent to the nucleic acids which encode said antisense nucleic acids, wherein the members of said set of primer pairs are designed such that each primer pair would yield an amplification product having a length distinguishable from the lengths of the amplification products from the other primer pairs if a strain comprising the nucleotide sequences complementary to said primer pair is present in said culture or collection of strains; and

determining the lengths of the amplification products obtained in said amplification reaction, wherein said culture comprises a strain in which a gene product whose activity or level is inhibited by a nucleic acid comprising a nucleotide sequence selected from the group consisting of SEQ ID NOs.: 1-6213 is overexpressed or underexpressed.

511.   A method for determining the extent to which each of a plurality of strains are present in a culture or collection of strains comprising:

obtaining a nucleic acid sample comprising nucleic acids from a culture or collection of strains wherein said culture or collection of strains comprises a plurality of strains which transcribe an antisense nucleic acid complementary to a different gene product which is required for proliferation of said organism;

performing an amplification reaction using a set of primer pairs which are complementary to nucleotide sequences within or adjacent to the nucleic acids which encode said antisense nucleic acids, wherein the members of said set of primer pairs are designed such that each primer pair would yield an amplification product having a length

distinguishable from the lengths of the amplification products from the other primer pairs if a strain comprising the nucleotide sequences complementary to said primer pair is present in said culture or collection of strains; and

determining the lengths of the amplification products obtained in said amplification reaction, wherein said culture comprises a strain in which a gene product encoded by a nucleic acid comprising a nucleotide sequence selected from the group consisting of SEQ ID NOs.: 6214-42397 is overexpressed or underexpressed.

512. A method for determining the extent to which each of a plurality of strains are present in a culture or collection of strains comprising:

obtaining a nucleic acid sample comprising nucleic acids from a culture or collection of strains wherein said culture or collection of strains comprises a plurality of strains which transcribe an antisense nucleic acid complementary to a different gene product which is required for proliferation of said organism;

performing an amplification reaction using a set of primer pairs which are complementary to nucleotide sequences within or adjacent to the nucleic acids which encode said antisense nucleic acids, wherein the members of said set of primer pairs are designed such that each primer pair would yield an amplification product having a length distinguishable from the lengths of the amplification products from the other primer pairs if a strain comprising the nucleotide sequences complementary to said primer pair is present in said culture or collection of strains; and

determining the lengths of the amplification products obtained in said amplification reaction, wherein said culture comprises a strain in which a gene product comprising an amino acid sequence selected from the group consisting of SEQ ID NOs.: 42938-78581 is overexpressed or underexpressed.

513. A method for determining the extent to which each of a plurality of strains are present in a culture or collection of strains comprising:

obtaining a nucleic acid sample comprising nucleic acids from a culture or collection of strains wherein said culture or collection of strains comprises a plurality of strains which transcribe an antisense nucleic acid complementary to a different gene product which is required for proliferation of said organism;

performing an amplification reaction using a set of primer pairs which are complementary to nucleotide sequences within or adjacent to the nucleic acids which encode said antisense nucleic acids, wherein the members of said set of primer pairs are designed such that each primer pair would yield an amplification product having a length distinguishable from the lengths of the amplification products from the other primer pairs if a strain comprising the nucleotide sequences complementary to said primer pair is present in said culture or collection of strains; and

determining the lengths of the amplification products obtained in said amplification reaction, wherein said culture comprises a strain in which a gene product selected from the group consisting of a gene product having at least 70% nucleotide sequence identity as determined using BLASTN version 2.0 with the default parameters to a gene product whose expression is inhibited by an antisense nucleic acid comprising a nucleotide sequence selected from the group consisting of SEQ ID NOs.: 1-6213, a gene product encoded by a nucleic acid having at least 70% nucleotide sequence identity as determined using BLASTN version 2.0 with the default parameters to a nucleic acid encoding a gene product whose expression is inhibited by an antisense nucleic acid comprising a nucleotide sequence selected from the group consisting of SEQ ID NOs: 1-6213, a gene product having at least 25% amino acid identity as determined using FASTA version 3.0t78 with the default parameters to a gene product whose expression is inhibited by an antisense nucleic acid comprising a nucleotide sequence selected from the group consisting of SEQ ID NOs.: 1-6213, a gene product encoded by a nucleic acid which hybridizes to a nucleic acid comprising a nucleotide sequence selected from the group consisting of SEQ ID NOs.: 1-6213 under stringent conditions, a gene product encoded by a nucleic acid which hybridizes to a nucleic acid comprising a nucleotide sequence selected from the group consisting of SEQ ID NOs.: 1-6213 under moderate conditions, and a gene product whose activity may be complemented by the gene product whose activity is inhibited by a nucleic acid comprising a nucleotide sequence selected from the group consisting of SEQ ID NOs: 1-6213 is overexpressed or underexpressed.

514.   A method for determining the extent to which each of a plurality of strains are present in a culture or collection of strains comprising:

obtaining a nucleic acid sample comprising nucleic acids from a culture or collection of strains wherein said culture or collection of strains comprises a plurality of strains which transcribe an antisense nucleic acid complementary to a different gene product which is required for proliferation of said organism;

performing an amplification reaction using a set of primer pairs which are complementary to nucleotide sequences within or adjacent to the nucleic acids which encode said antisense nucleic acids, wherein the members of said set of primer pairs are designed such that each primer pair would yield an amplification product having a length distinguishable from the lengths of the amplification products from the other primer pairs if a strain comprising the nucleotide sequences complementary to said primer pair is present in said culture or collection of strains; and

determining the lengths of the amplification products obtained in said amplification reaction, wherein said culture comprises a strain in which a gene product encoded by a nucleic acid comprising a nucleotide sequence selected from the group consisting of a nucleic acid comprising a nucleic acid having at least 70% nucleotide sequence identity as

determined using BLASTN version 2.0 with the default parameters to a nucleotide sequence selected from the group consisting of SEQ ID NOS.: 6214-42397, a nucleic acid comprising a nucleotide sequence which hybridizes to a sequence selected from the group consisting of SEQ ID NOS.: 6214-42397 under stringent conditions, and a nucleic acid comprising a nucleotide sequence which hybridizes to a nucleotide sequence selected from the group consisting of SEQ ID NOS.: 6214-42397 under moderate conditions is overexpressed or underexpressed.

515.   A method for determining the extent to which each of a plurality of strains are present in a culture or collection of strains comprising:

obtaining a nucleic acid sample comprising nucleic acids from a culture or collection of strains wherein said culture or collection of strains comprises a plurality of strains which transcribe an antisense nucleic acid complementary to a different gene product which is required for proliferation of said organism;

performing an amplification reaction using a set of primer pairs which are complementary to nucleotide sequences within or adjacent to the nucleic acids which encode said antisense nucleic acids, wherein the members of said set of primer pairs are designed such that each primer pair would yield an amplification product having a length distinguishable from the lengths of the amplification products from the other primer pairs if a strain comprising the nucleotide sequences complementary to said primer pair is present in said culture or collection of strains; and

determining the lengths of the amplification products obtained in said amplification reaction, wherein said culture comprises a strain in which a gene product comprising a polypeptide selected from the group consisting of a polypeptide having at least 25% amino acid identity as determined using FASTA version 3.0t78 to a polypeptide selected from the group consisting of SEQ ID NOs.: 42938-78581 and a polypeptide whose activity may be complemented by a polypeptide selected from the group consisting of SEQ ID NOs: 42938-78581 is overexpressed or underexpressed.

516.   The method of Paragraph 510, 511, 512, 513, 514 or 515, wherein one member of each primer pair for each of said genes is labeled with a detectable dye.

517.   The method of Paragraph 510, 511, 512, 513, 514 or 515, wherein:

said nucleic acid sample is divided into N aliquots; and

said amplification reaction is performed on each aliquot using primer pairs complementary to nucleotide sequences within or adjacent to 1/N of the genes which encode said gene products, wherein one of the members of each primer pair in each aliquot is labeled with a dye and wherein the dyes on the primers in each aliquot are distinguishable from one another.

518.   The method of Paragraph 517, further comprising pooling the amplification products from each of the aliquots prior to determining the lengths of the amplification products.

519.   A method for determining the extent to which each of a plurality of strains are present in a culture or collection of strains comprising:

obtaining a nucleic acid sample comprising nucleic acids from a culture or collection of strains wherein said culture or collection of strains comprises a plurality of strains which overexpress or underexpress a different gene product which is required for proliferation of said organism;

performing an amplification reaction using primer pairs which are complementary to nucleotide sequences within or adjacent to the genes which encode said gene products, wherein said primer pairs are designed such that each primer pair would yield an amplification product which is distinguishable from the amplification products produced by the other primer pairs on the a basis selected from the group consisting of length, detectable label and both length and detectable label if a strain comprising the nucleotide sequences complementary to said primer pair is present in said culture or collection of strains; and

identifying the amplification products obtained in said amplification reaction, wherein said culture comprises a strain in which a gene product whose activity or level is inhibited by a nucleic acid comprising a nucleotide sequence selected from the group consisting of SEQ ID NOs.: 1-6213 is overexpressed or underexpressed.

520.   A method for determining the extent to which each of a plurality of strains are present in a culture or collection of strains comprising:

obtaining a nucleic acid sample comprising nucleic acids from a culture or collection of strains wherein said culture or collection of strains comprises a plurality of strains which overexpress or underexpress a different gene product which is required for proliferation of said organism;

performing an amplification reaction using primer pairs which are complementary to nucleotide sequences within or adjacent to the genes which encode said gene products, wherein said primer pairs are designed such that each primer pair would yield an amplification product which is distinguishable from the amplification products produced by the other primer pairs on the a basis selected from the group consisting of length, detectable label and both length and detectable label if a strain comprising the nucleotide sequences complementary to said primer pair is present in said culture or collection of strains; and

identifying the amplification products obtained in said amplification reaction, wherein said culture comprises a strain in which a gene product encoded by a nucleic acid comprising a nucleotide sequence selected from the group consisting of SEQ ID NOs.: 6214-42397 is overexpressed or underexpressed.

521.   A method for determining the extent to which each of a plurality of strains are present in a culture or collection of strains comprising:

obtaining a nucleic acid sample comprising nucleic acids from a culture or collection of strains wherein said culture or collection of strains comprises a plurality of

strains which overexpress or underexpress a different gene product which is required for proliferation of said organism;

performing an amplification reaction using primer pairs which are complementary to nucleotide sequences within or adjacent to the genes which encode said gene products,

5   wherein said primer pairs are designed such that each primer pair would yield an amplification product which is distinguishable from the amplification products produced by the other primer pairs on the a basis selected from the group consisting of length, detectable label and both length and detectable label if a strain comprising the nucleotide sequences complementary to said primer pair is present in said culture or collection of strains; and

10   identifying the amplification products obtained in said amplification reaction, wherein said culture comprises a strain in which a gene product comprising an amino acid sequence selected from the group consisting of SEQ ID NOs.: 42938-78581 is overexpressed or underexpressed.

522.   A method for determining the extent to which each of a plurality of strains are
15   present in a culture or collection of strains comprising:

obtaining a nucleic acid sample comprising nucleic acids from a culture or collection of strains wherein said culture or collection of strains comprises a plurality of strains which overexpress or underexpress a different gene product which is required for proliferation of said organism;

20   performing an amplification reaction using primer pairs which are complementary to nucleotide sequences within or adjacent to the genes which encode said gene products, wherein said primer pairs are designed such that each primer pair would yield an amplification product which is distinguishable from the amplification products produced by the other primer pairs on the a basis selected from the group consisting of length, detectable
25   label and both length and detectable label if a strain comprising the nucleotide sequences complementary to said primer pair is present in said culture or collection of strains; and

identifying the amplification products obtained in said amplification reaction, wherein said culture comprises a strain in which a gene product selected from the group consisting of a gene product having at least 70% nucleotide sequence identity as determined
30   using BLASTN version 2.0 with the default parameters to a gene product whose expression is inhibited by an antisense nucleic acid comprising a nucleotide sequence selected from the group consisting of SEQ ID NOs.: 1-6213, a gene product encoded by a nucleic acid having at least 70% nucleotide sequence identity as determined using BLASTN version 2.0 with the default parameters to a nucleic acid encoding a gene product whose expression is
35   inhibited by an antisense nucleic acid comprising a nucleotide sequence selected from the group consisting of SEQ ID NOs: 1-6213, a gene product having at least 25% amino acid identity as determined using FASTA version 3.0t78 with the default parameters to a gene product whose expression is inhibited by an antisense nucleic acid comprising a nucleotide

sequence selected from the group consisting of SEQ ID NOs.: 1-6213, a gene product encoded by a nucleic acid which hybridizes to a nucleic acid comprising a nucleotide sequence selected from the group consisting of SEQ ID NOs.: 1-6213 under stringent conditions, a gene product encoded by a nucleic acid which hybridizes to a nucleic acid comprising a nucleotide sequence selected from the group consisting of SEQ ID NOs.: 1-6213 under moderate conditions, and a gene product whose activity may be complemented by the gene product whose activity is inhibited by a nucleic acid comprising a nucleotide sequence selected from the group consisting of SEQ ID NOs: 1-6213 is overexpressed or underexpressed.

523.   A method for determining the extent to which each of a plurality of strains are present in a culture or collection of strains comprising:

obtaining a nucleic acid sample comprising nucleic acids from a culture or collection of strains wherein said culture or collection of strains comprises a plurality of strains which overexpress or underexpress a different gene product which is required for proliferation of said organism;

performing an amplification reaction using primer pairs which are complementary to nucleotide sequences within or adjacent to the genes which encode said gene products, wherein said primer pairs are designed such that each primer pair would yield an amplification product which is distinguishable from the amplification products produced by the other primer pairs on the a basis selected from the group consisting of length, detectable label and both length and detectable label if a strain comprising the nucleotide sequences complementary to said primer pair is present in said culture or collection of strains; and

identifying the amplification products obtained in said amplification reaction, wherein said culture comprises a strain in which a gene product encoded by a nucleic acid comprising a nucleotide sequence selected from the group consisting of a nucleic acid comprising a nucleic acid having at least 70% nucleotide sequence identity as determined using BLASTN version 2.0 with the default parameters to a nucleotide sequence selected from the group consisting of SEQ ID NOS.: 6214-42397, a nucleic acid comprising a nucleotide sequence which hybridizes to a sequence selected from the group consisting of SEQ ID NOS.: 6214-42397 under stringent conditions, and a nucleic acid comprising a nucleotide sequence which hybridizes to a nucleotide sequence selected from the group consisting of SEQ ID NOS.: 6214-42397 under moderate conditions is overexpressed or underexpressed.

524.   A method for determining the extent to which each of a plurality of strains are present in a culture or collection of strains comprising:

obtaining a nucleic acid sample comprising nucleic acids from a culture or collection of strains wherein said culture or collection of strains comprises a plurality of

strains which overexpress or underexpress a different gene product which is required for proliferation of said organism;

5

performing an amplification reaction using primer pairs which are complementary to nucleotide sequences within or adjacent to the genes which encode said gene products, wherein said primer pairs are designed such that each primer pair would yield an amplification product which is distinguishable from the amplification products produced by the other primer pairs on the a basis selected from the group consisting of length, detectable label and both length and detectable label if a strain comprising the nucleotide sequences complementary to said primer pair is present in said culture or collection of strains; and

10

15

identifying the amplification products obtained in said amplification reaction, wherein said culture comprises a strain in which a gene product comprising a polypeptide selected from the group consisting of a polypeptide having at least 25% amino acid identity as determined using FASTA version 3.0t78 to a polypeptide selected from the group consisting of SEQ ID NOs.: 42938-78581 and a polypeptide whose activity may be complemented by a polypeptide selected from the group consisting of SEQ ID NOs: 42938-78581 is overexpressed or underexpressed.

525.   The method of Paragraph 519, 520, 521, 522, 523 or 524, wherein said primer pairs are divided into at least two sets, each primer pair comprises a primer which is labeled with a distinguishable dye, and the distinguishable dye used to label each set of primer pairs is

20   distinguishable from the dye used to label the other sets of primer pairs.

526.   The method of Paragraph 519, 520, 521, 522, 523 or 524, wherein:

said nucleic acid sample is divided into N aliquots; and

25

said amplification reaction is performed on each aliquot using primer pairs complementary to nucleotide sequences within or adjacent to 1/N of the genes which encode said gene products, wherein one of the members of each primer pair in each aliquot is labeled with a dye and wherein the dyes on the primers in each aliquot are distinguishable from one another.

527.   The method of Paragraph 526, further comprising pooling the amplification products from each of the aliquots prior to determining the lengths of the amplification products.

30   528.   The method of Paragraph 519, 520, 521, 522, 523 or 524, wherein the native promoters of said genes which encode said gene products have been replaced with a regulatable promoter and one of the primers in said primer pairs is complementary to a nucleotide sequence within said regulatable promoter.

529.   The method of Paragraph 528, wherein the native promoters for each of said genes

35   were replaced with the same regulatable promoter.

530.   The method of Paragraph 528, wherein more than one regulatable promoter was used to replace the promoters of said genes such that some of said genes are under the control of a different regulatable promoter.

Definitions

By "biological pathway" is meant any discrete cell function or process that is carried out by a gene product or a subset of gene products. Biological pathways include anabolic, catabolic, enzymatic, biochemical and metabolic pathways as well as pathways involved in the production of

5   cellular structures such as cell walls. Biological pathways that are usually required for proliferation of cells or microorganisms include, but are not limited to, cell division, DNA synthesis and replication, RNA synthesis (transcription), protein synthesis (translation), protein processing, protein transport, fatty acid biosynthesis, electron transport chains, cell wall synthesis, cell membrane production, synthesis and maintenance, and the like.

10   By "inhibit activity of a gene or gene product" is meant having the ability to interfere with the function of a gene or gene product in such a way as to decrease expression of the gene, in such a way as to reduce the level or activity of a product of the gene or in such a way as to inhibit the interaction of the gene or gene product with other biological molecules required for its activity. Agents which inhibit the activity of a gene include agents that inhibit transcription of the gene,

15   agents that inhibit processing of the transcript of the gene, agents that reduce the stability of the transcript of the gene, and agents that inhibit translation of the mRNA transcribed from the gene. In microorganisms, agents which inhibit the activity of a gene can act to decrease expression of the operon in which the gene resides or alter the folding or processing of operon RNA so as to reduce the level or activity of the gene product. The gene product can be a non-translated RNA such as

20   ribosomal RNA, a translated RNA (mRNA) or the protein product resulting from translation of the gene mRNA. Of particular utility to the present invention are antisense RNAs that have activities against the operons or genes to which they specifically hybridze.

By "activity against a gene product" is meant having the ability to inhibit the function or to reduce the level or activity of the gene product in a cell. This includes, but is not limited to,

25   inhibiting the enzymatic activity of the gene product or the ability of the gene product to interact with other biological molecules required for its activity, including inhibiting the gene product's assembly into a multimeric structure.

By "activity against a protein" is meant having the ability to inhibit the function or to reduce the level or activity of the protein in a cell. This includes, but is not limited to, inhibiting the

30   enzymatic activity of the protein or the ability of the protein to interact with other biological molecules required for its activity, including inhibiting the protein's assembly into a multimeric structure.

By "activity against a nucleic acid" is meant having the ability to inhibit the function or to reduce the level or activity of the nucleic acid in a cell. This includes, but is not limited to,

35   inhibiting the ability of the nucleic acid interact with other biological molecules required for its activity, including inhibiting the nucleic acid's assembly into a multimeric structure.

By "activity against a gene" is meant having the ability to inhibit the function or expression of the gene in a cell. This includes, but is not limited to, inhibiting the ability of the gene to interact with other biological molecules required for its activity.

By "activity against an operon" is meant having the ability to inhibit the function or reduce
5   the level of one or more products of the operon in a cell. This includes, but is not limited to, inhibiting the enzymatic activity of one or more products of the operon or the ability of one or more products of the operon to interact with other biological molecules required for its activity.

By "antibiotic" is meant an agent which inhibits the proliferation of a cell or microorganism.

10   By "E. coli or Escherichia coli" is meant Escherichia coli or any organism previously categorized as a species of Shigella including Shigella boydii, Shigella flexneri, Shigella dysenteriae, Shigella sonnei, Shigella 2A.

By "homologous coding nucleic acid" is meant a nucleic acid homologous to a nucleic acid encoding a gene product whose activity or level is inhibited by a nucleic acid selected from the
15   group consisting of SEQ ID NOs.: 1-6213 or a portion thereof.   In some embodiments, the homologous coding nucleic acid may have at least 97%, at least 95%, at least 90%, at least 85%, at least 80%, or at least 70% nucleotide sequence identity to a nucleotide sequence selected from the group consisting of SEQ ID NOS.: 6214-42,397 and fragments comprising at least 10, 15, 20, 25, 30, 35, 40, 50, 75, 100, 150, 200, 300, 400, or 500 consecutive nucleotides thereof.   In other
20   embodiments the homologous coding nucleic acids may have at least 97%, at least 95%, at least 90%, at least 85%, at least 80%, or at least 70% nucleotide sequence identity to a nucleotide sequence selected from the group consisting of the nucleotide sequences complementary to one of SEQ ID NOs.: 1-6213 and fragments comprising at least 10, 15, 20, 25, 30, 35, 40, 50, 75, 100, 150, 200, 300, 400, or 500 consecutive nucleotides thereof. Identity may be measured using BLASTN
25   version 2.0 with the default parameters or tBLASTX with the default parameters. (Altschul, S.F. et al. Gapped BLAST and PSI-BLAST: A New Generation of Protein Database Search Programs, Nucleic Acid Res. 25: 3389-3402 (1997). Alternatively a "homologuous coding nucleic acid" could be identified by membership of the gene of interest to a functional orthologue cluster. All other members of that orthologue cluster would be considered homologues. Such a library of
30   functional orthologue clusters can be found at http://www.ncbi.nlm.nih.gov/COG. A gene can be classified into a cluster of orthologous groups or COG by using the COGNITOR program available at the above web site, or by direct BLASTP comparison of the gene of interest to the members of the COGs and analysis of these results as described by Tatusov, R.L., Galperin, M.Y., Natale, D. A. and Koonin, E.V. (2000) The COG database: a tool for genome-scale analysis of protein functions
35   and evolution. Nucleic Acids Research v. 28 n. 1, pp33-36.

Homologous coding nucleic acids and the homologous polypeptides which they encode may also be identified using a "reciprocal" best-hit analysis. To facilitate the identification of homologous coding nucleic acids and homologous polypeptides, paralogous genes within each of

51 organisms are identified and clustered prior to comparison to other organisms. Briefly, the polypeptide sequence of each polypeptide encoded by each open reading frame (ORF) in a given organism is compared to the polypeptide sequence encoded by every other ORF for that organism for each of the 51 pathogenic organisms (PathoSeq Sept 2001 release) using BLASTP 2.09

5 algorithm without filtering. Simultaneously, the polypeptide sequence encoded by each ORF of an organism is compared to the polypeptide sequences encoded by each of the ORFs in the remaining 51 organisms. Those polypeptides within a single organism that shared a higher degree of sequence identity to one another than to polypeptide sequences obtained from any other organisms are clustered as "paralog" sequences for "reciprocal" best-hit analysis.

10 For each reference organism, the 50 homologous coding nucleic acids (and the 50 homologous polypeptides which they encode) can be determined by identifying the ORFs in each of the 50 comparison organisms which encode a polypeptide sharing the highest degree of amino acid sequence identity to the polypeptide encoded by the ORF from the reference organism. The accuracy of the identification of the predicted homologous coding nucleic acids (and the

15 homologous polypeptides which they encode) is confirmed by a "reciprocal" BLAST analysis in which the polypeptide sequence of the predicted homologous polypeptide is compared against the polypeptides encoded by each of the ORFS in the reference organism using BLASTP 2.09 algorithm without filtering. Only those polypeptides that share the highest degree of amino acid sequence identity in each portion of the two-way comparison are retained for further analysis.

20 The term "homologous coding nucleic acid" also includes nucleic acids comprising nucleotide sequences which encode polypeptides having at least 99%, 95%, at least 90%, at least 85%, at least 80%, at least 70%, at least 60%, at least 50%, at least 40% or at least 25% maino acid identity or similarity to a polypeptide comprising the amino acid sequence of one of SEQ ID NOs: 42,398-78,581 or to a polypeptpide whose expression is inhibited by a nucleic acid comprising a

25 nucleotide sequence of one of SEQ ID NOs: 1-6213 or fragments comprising at least 5, 10, 15, 20, 25, 30, 35, 40, 50, 75, 100, or 150 consecutive amino acids thereof as determined using the FASTA version 3.0t78 algorithm with the default parameters. Alternatively, protein identity or similarity may be identified using BLASTP with the default parameters, BLASTX with the default parameters, TBLASTN with the default parameters, or tBLASTX with the default parameters.

30 (Altschul, S.F. et al. Gapped BLAST and PSI-BLAST: A New Generation of Protein Database Search Programs, Nucleic Acid Res. 25: 3389-3402 (1997).

Additionally, homologous coding nucleic acids and the homologous polypeptides which they encode may be identified using a "reciprocal" best-hit analysis. To facilitate the identification of homologous coding nucleic acids and homologous polypeptides, paralogous genes within each of

35 51 organisms are identified and clustered prior to comparison to other organisms. Briefly, the polypeptide sequence of each polypeptide encoded by each open reading frame (ORF) in a given organism is compared to the polypeptide sequence encoded by every other ORF for that organism for each of the 51 pathogenic organisms (PathoSeq Sept 2001 release) using BLASTP 2.09

algorithm without filtering. Simultaneously, the polypeptide sequence encoded by each ORF of an organism is compared to the polypeptide sequences encoded by each of the ORFs in the remaining 51 organisms. Those polypeptides within a single organism that shared a higher degree of sequence identity to one another than to polypeptide sequences obtained from any other organisms are

5   clustered as "paralog" sequences for "reciprocal" best-hit analysis.

For each reference organism, the 50 homologous coding nucleic acids (and the 50 homologous polypeptides which they encode) can be determined by identifying the ORFs in each of the 50 comparison organisms which encode a polypeptide sharing the highest degree of amino acid sequence identity to the polypeptide encoded by the ORF from the reference organism. The

10   accuracy of the identification of the predicted homologous coding nucleic acids (and the homologous polypeptides which they encode) is confirmed by a "reciprocal" BLAST analysis in which the polypeptide sequence of the predicted homologous polypeptide is compared against the polypeptides encoded by each of the ORFS in the reference organism using BLASTP 2.09 algorithm without filtering. Only those polypeptides that share the highest degree of amino acid

15   sequence identity in each portion of the two-way comparison are retained for further analysis.

The term "homologous coding nucleic acid" also includes coding nucleic acids which hybridize under stringent conditions to a nucleic acid selected from the group consisting of the nucleotide sequences complementary to one of SEQ ID NOS.: 6214-42,397 and coding nucleic acids comprising nucleotide sequences which hybridize under stringent conditions to a fragment

20   comprising at least 10, 15, 20, 25, 30, 35, 40, 50, 75, 100, 150, 200, 300, 400, or 500 consecutive nucleotides of the sequences complementary to one of SEQ ID NOS.: 6214-42,397. As used herein, "stringent conditions" means hybridization to filter-bound nucleic acid in 6xSSC at about 45°C followed by one or more washes in 0.1xSSC/0.2% SDS at about 68°C. Other exemplary stringent conditions may refer, e.g., to washing in 6xSSC/0.05% sodium pyrophosphate at 37°C,

25   48°C, 55°C, and 60°C as appropriate for the particular probe being used.

The term "homologous coding nucleic acid" also includes coding nucleic acids comprising nucleotide sequences which hybridize under moderate conditions to a nucleotide sequence selected from the group consisting of the sequences complementary to one of SEQ ID NOS.: 6214-42,397 and coding nucleic acids comprising nucleotide sequences which hybridize under moderate

30   conditions to a fragment comprising at least 10, 15, 20, 25, 30, 35, 40, 50, 75, 100, 150, 200, 300, 400, or 500 consecutive nucleotides of the sequences complementary to one of SEQ ID NOS.: 6214-42,397. As used herein, "moderate conditions" means hybridization to filter-bound DNA in 6x sodium chloride/sodium citrate (SSC) at about 45°C followed by one or more washes in 0.2xSSC/0.1% SDS at about 42-65°C.

35   The term "homologous coding nucleic acids" also includes nucleic acids comprising nucleotide sequences which encode a gene product whose activity may be complemented by a gene encoding a gene product whose activity is inhibited by a nucleic acid comprising a nucleotide sequence selected from the group consisting of SEQ ID NOs.: 1-6213. In some embodiments, the

homologous coding nucleic acids may encode a gene product whose activity is complemented by the gene product encoded by a nucleic acid comprising a nucleotide sequence selected from the group consisting of SEQ ID NOS.: 6214-42,397. In other embodiments, the homologous coding nucleic acids may comprise a nucleotide sequence encode a gene product whose activity is 5   complemented by one of the polypeptides of SEQ ID NOs. 42,398-78,581.

The term "homologous antisense nucleic acid" includes nucleic acids comprising a nucleotide sequence having at least 97%, at least 95%, at least 90%, at least 85%, at least 80%, or at least 70% nucleotide sequence identity to a nucleotide sequence selected from the group consisting of one of the sequences of SEQ ID NOS. 1-6213 and fragments comprising at least 10, 15, 20, 25, 10   30, 35, 40, 50, 75, 100, 150, 200, 300, 400, or 500 consecutive nucleotides thereof. Homologous antisense nucleic acids may also comprising nucleotide sequences which have at least 97%, at least 95%, at least 90%, at least 85%, at least 80%, or at least 70% nucleotide sequence identity to a nucleotide sequence selected from the group consisting of the sequences complementary to one of sequences of SEQ ID NOS.: 6214-42,397 and fragments comprising at least 10, 15, 20, 25, 30, 35, 15   40, 50, 75, 100, 150, 200, 300, 400, or 500 consecutive nucleotides thereof. Nucleic acid identity may be determined as described above.

The term "homologous antisense nucleic acid" also includes antisense nucleic acids comprising nucleotide sequences which hybridize under stringent conditions to a nucleotide sequence complementary to one of SEQ ID NOs.: 1-6213 and antisense nucleic acids comprising 20   nucleotide sequences which hybridize under stringent conditions to a fragment comprising at least 10, 15, 20, 25, 30, 35, 40, 50, 75, 100, 150, 200, 300, 400, or 500 consecutive nucleotides of the sequence complementary to one of SEQ ID NOs. 1-6213. Homologous antisense nucleic acids also include antisense nucleic acids comprising nucleotide sequences which hybridize under stringent conditions to a nucleotide sequence selected from the group consisting of SEQ ID NOS.: 6214- 25   42,397 and antisense nucleic acids comprising nucleotide sequences which hybridize under stringent conditions to a fragment comprising at least 10, 15, 20, 25, 30, 35, 40, 50, 75, 100, 150, 200, 300, 400, or 500 consecutive nucleotides of one of SEQ ID NOS.: 6214-42,397.

The term "homologous antisense nucleic acid" also includes antisense nucleic acids comprising nucleotide sequences which hybridize under moderate conditions to a nucleotide 30   sequence complementary to one of SEQ ID NOs.: 1-6213 and antisense nucleic acids comprising nucleotide seuqences which hybridize under moderate conditions to a fragment comprising at least 10, 15, 20, 25, 30, 35, 40, 50, 75, 100, 150, 200, 300, 400, or 500 consecutive nucleotides of the sequence complementary to one of SEQ ID NOs. 1-6213. Homologous antisense nucleic acids also include antisense nucleic acids comprising nucleotide seuqences which hybridize under moderate 35   conditions to a nucleotide sequence selected from the group consisting of SEQ ID NOS.: 6214- 42,397 and antisense nucleic acids which comprising nucleotide sequences hybridize under moderate conditions to a fragment comprising at least 10, 15, 20, 25, 30, 35, 40, 50, 75, 100, 150, 200, 300, 400, or 500 consecutive nucleotides of one of SEQ ID NOS.: 6214-42,397.

By "homologous polypeptide" is meant a polypeptide homologous to a polypeptide whose activity or level is inhibited by a nucleic acid comprising a nucleotide sequence selected from the group consisting of SEQ ID NOs.: 1-6213 or by a homologous antisense nucleic acid. The term "homologous polypeptide" includes polypeptides having at least 99%, 95%, at least 90%, at least

5   85%, at least 80%, at least 70%, at least 60%, at least 50%, at least 40% or at least 25% amino acid identity or similarity to a polypeptide whose activity or level is inhibited by a nucleic acid selected from the group consisting of SEQ ID NOs: 1-6213 or by a homologous antisense nucleic acid, or polypeptides having at least 99%, 95%, at least 90%, at least 85%, at least 80%, at least 70%, at least 60%, at least 50%, at least 40% or at least 25% amino acid identity or similarity to a

10   polypeptide to a fragment comprising at least 5, 10, 15, 20, 25, 30, 35, 40, 50, 75, 100, or 150 consecutive amino acids of a polypeptide whose activity or level is inhibited by a nucleic acid selected from the group consisting of SEQ ID NOs.: 1-6213 or by a homologous antisense nucleic acid. Identity or similarity may be determined using the FASTA version 3.0t78 algorithm with the default parameters. Alternatively, protein identity or similarity may be identified using BLASTP

15   with the default parameters, BLASTX with the default parameters, or TBLASTN with the default parameters. (Altschul, S.F. et al. Gapped BLAST and PSI-BLAST: A New Generation of Protein Database Search Programs, Nucleic Acid Res. 25: 3389-3402 (1997). Additionally, homologous coding nucleic acids and the homologous polypeptides which they encode may be identified using a "reciprocal" best-hit analysis. To facilitate the identification of homologous coding nucleic acids

20   and homologous polypeptides, paralogous genes within each of 51 organisms are identified and clustered prior to comparison to other organisms. Briefly, the polypeptide sequence of each polypeptide encoded by each open reading frame (ORF) in a given organism is compared to the polypeptide sequence encoded by every other ORF for that organism for each of the 51 pathogenic organisms (PathoSeq Sept 2001 release) using BLASTP 2.09 algorithm without filtering.

25   Simultaneously, the polypeptide sequence encoded by each ORF of an organism is compared to the polypeptide sequences encoded by each of the ORFs in the remaining 51 organisms. Those polypeptides within a single organism that shared a higher degree of sequence identity to one another than to polypeptide sequences obtained from any other organisms are clustered as "paralog" sequences for "reciprocal" best-hit analysis.

30   For each reference organism, the 50 homologous coding nucleic acids (and the 50 homologous polypeptides which they encode) can be determined by identifying the ORFs in each of the 50 comparison organisms which encode a polypeptide sharing the highest degree of amino acid sequence identity to the polypeptide encoded by the ORF from the reference organism. The accuracy of the identification of the predicted homologous coding nucleic acids (and the

35   homologous polypeptides which they encode) is confirmed by a "reciprocal" BLAST analysis in which the polypeptide sequence of the predicted homologous polypeptide is compared against the polypeptides encoded by each of the ORFS in the reference organism using BLASTP 2.09

algorithm without filtering. Only those polypeptides that share the highest degree of amino acid sequence identity in each portion of the two-way comparison are retained for further analysis.

The term homologous polypeptide also includes polypeptides having at least 99%, 95%, at least 90%, at least 85%, at least 80%, at least 70%, at least 60%, at least 50%, at least 40% or at
5   least 25% amino acid identity or similarity to a polypeptide selected from the group consisting of SEQ ID NOs: 42,398-78,581 and polypeptides having at least 99%, 95%, at least 90%, at least 85%, at least 80%, at least 70%, at least 60%, at least 50%, at least 40% or at least 25% amino acid identity or similarity to a fragment comprising at least 5, 10, 15, 20, 25, 30, 35, 40, 50, 75, 100, or 150 consecutive amino acids of a polypeptide selected from the group consisting of SEQ ID NOs:
10   42,398-78,581.

The invention also includes polynucleotides, preferably DNA molecules, that hybridize to one of the nucleic acids of SEQ ID NOs.: 1-6213, SEQ ID NOs.: 6214-42,397 or the complements of any of the preceding nucleic acids. Such hybridization may be under stringent or moderate conditions as defined above or under other conditions which permit specific hybridization. The
15   nucleic acid molecules of the invention that hybridize to these DNA sequences include oligodeoxynucleotides ("oligos") which hybridize to the target gene under highly stringent or stringent conditions. In general, for oligos between 14 and 70 nucleotides in length the melting temperature (Tm) is calculated using the formula:

$$Tm\ (^{\circ}C) = 81.5 + 16.6(log[monovalent\ cations\ (molar)] + 0.41\ (\%\ G+C) - (500/N)$$

20   where N is the length of the probe. If the hybridization is carried out in a solution containing formamide, the melting temperature may be calculated using the equation:

$$Tm(^{\circ}C) = 81.5 + 16.6(log[monovalent\ cations\ (molar)] + 0.41(\%\ G+C) - (0.61)$$

$$(\%\ formamide) - (500/N)$$

where N is the length of the probe. In general, hybridization is carried out at about 20-25
25   degrees below Tm (for DNA-DNA hybrids) or about 10-15 degrees below Tm (for RNA-DNA hybrids).

Other hybridization conditions are apparent to those of skill in the art (see, for example, Ausubel, F.M. et al., eds., 1989, Current Protocols in Molecular Biology, Vol. I, Green Publishing Associates, Inc. and John Wiley & Sons, Inc., New York, at pp. 6.3.1-6.3.6 and 2.10.3.
30   The term, Salmonella, is the generic name for a large group of gram negative enteric bacteria that are closely related to Escherichia coli. The diseases caused by Salmonella are often due to contamination of foodstuffs or the water supply and affect millions of people each year. Traditional methods of Salmonella taxonomy were based on assigning a separate species name to each serologically distinguishable strain (Kauffmann, F 1966 The bacteriology of the
35   Enterobacteriaceae. Munksgaard, Copenhagen). Serology of Salmonella is based on surface antigens (O [somatic] and H [flagellar]). Over 2,400 serotypes or serovars of Salmonella are known (Popoff, et al. 2000 Res. Microbiol. 151:63-65). Therefore, each serotype was considered to

be a separate species and often given names, accordingly (e.g. *S. paratyphi*, *S. typhimurium*, *S. typhi*, *S. enteriditis*, etc.).

However, by the 1970s and 1980s it was recognized that this system was not only cumbersome, but also inaccurate. Then, many *Salmonella* species were lumped into a single

5   species (all serotypes and subgenera I, II, and IV and all serotypes of *Arizona*) with a second subspecies, *S. bongorii* also recognized (Crosa, et al., 1973, J. Bacteriol. 115:307-315). Though species designations are based on the highly variable surface antigens, the *Salmonella* are very similar otherwise with a major exception being pathogenicity determinants.

There has been some debate on the correct name for the *Salmonella* species. Currently

10   (Brenner, et al. 2000 J. Clin. Microbiol. 38:2465-2467), the accepted name is *Salmonella enterica*. *S. enterica* is divided into six subspecies (I, *S. enterica* subsp. *enterica*; II, *S. enterica*, subsp. *salamae*; IIIa, *S. enterica* subsp. *arizonae*; IIIb, *S. enterica* subsp. *diarizonae*; IV, *S. enterica* subsp. *houtenae*; and VI, *S. enterica* subsp. *indica*). Within subspecies I, serotypes are used to distinguish each of the serotypes or serovars (e.g. *S. enterica* serotype Enteriditis, *S. enterica* serotype

15   Typhimurium, *S. enterica* serotype Typhi, and *S. enterica* serotype Choleraesuis, etc.). Current convention is to spell this out on first usage (*Salmonella enterica* ser. Typhimurium) and then use an abbreviated form (*Salmonella* Typhimurium or *S.* Typhimurium). Note, the genus and species names (*Salmonella enterica*) are italicized but not the serotype/serovar name (Typhimurium). Because the taxonomic committees have yet to officially approve of the actual species name, this

20   latter system is what is employed by the CDC (Brenner, et al. 2000 J. Clin. Microbiol. 38:2465-2467). Due to the concerns of both taxonomic priority and medical importance, some of these serotypes might ultimately receive full species designations (*S.typhi* would be the most notable).

Therefore, as used herein "*Salmonella enterica* or *S. enterica*" includes serovars Typhi, Typhimurium, Paratyphi, Choleraesuis, etc." However, appeals of the "official" name are in process

25   and the taxonomic designations may change (*S. choleraesuis* is the species name that could replace *S. enterica* based solely on priority).

By "identifying a compound" is meant to screen one or more compounds in a collection of compounds such as a combinatorial chemical library or other library of chemical compounds or to characterize a single compound by testing the compound in a given assay and determining whether

30   it exhibits the desired activity.

By "inducer" is meant an agent or solution which, when placed in contact with a cell or microorganism, increases transcription, or inhibitor and/or promoter clearance/fidelity, from a desired promoter.

As used herein, "nucleic acid" means DNA, RNA, or modified nucleic acids. Thus, the

35   terminology "the nucleic acid of SEQ ID NO: X" or "the nucleic acid comprising the nucleotide sequence" includes both the DNA sequence of SEQ ID NO: X and an RNA sequence in which the thymidines in the DNA sequence have been substituted with uridines in the RNA sequence and in which the deoxyribose backbone of the DNA sequence has been substituted with a ribose backbone

in the RNA sequence. Modified nucleic acids are nucleic acids having nucleotides or structures which do not occur in nature, such as nucleic acids in which the internucleotide phosphate residues with methylphosphonates, phosphorothioates, phosphoramidates, and phosphate esters. Nonphosphate internucleotide analogs such as siloxane bridges, carbonate brides, thioester bridges, as well as many others known in the art may also be used in modified nucleic acids.   Modified nucleic acids may also comprise, α-anomeric nucleotide units and modified nucleotides such as 1,2-dideoxy-d-ribofuranose, 1,2-dideoxy-1-phenylribofuranose, and N^4, N^4-ethano-5-methyl-cytosine are contemplated for use in the present invention.   Modified nucleic acids may also be peptide nucleic acids in which the entire deoxyribose-phosphate backbone has been exchanged with a chemically completely different, but structurally homologous, polyamide (peptide) backbone containing 2-aminoethyl glycine units.

As used herein, "sub-lethal" means a concentration of an agent below the concentration required to inhibit all cell growth.

Brief Description of the Drawings

Figure 1A illustrates a method for replacing a promoter using a promoter replacement cassette comprising a 5' region homologous to the sequence which is 5' of the natural promoter in the chromosome, the promoter which is to replace the chromosomal promoter and a 3' region which is homologous to sequences 3' of the natural promoter in the chromosome.

Figure 1B illustrates a method for replacing a promoter using a promoter replacement cassette comprising a nucleic acid encoding an identifiable or selectable marker disposed between the 5' region which is homologous to the sequence 5' of the natural promoter and the promoter which is to replace the chromosomal promoter and a transcriptional terminator 3' of the gene encoding an identifiable or selectable marker.

Figures 2A and 2B illustrate one method for identifying amplification products which are underrepresented or overrepresented in a culture.

Figures 3A and 3B illustrate another method for identifying amplification products which are underrepresented or overrepresented in a culture.

Figure 4 illustrates the results of a hybridization analysis where the antisense nucleic acid expressed by a strain in the culture is not complementary to all or a portion of the gene encoding the target of the compound (i.e. a nonspecific strain).

Figure 5 illustrates the results of a hybridization analysis where the antisense nucleic acid expressed by a strain in the culture is complementary to all or a portion of the gene encoding the target of the compound; the hybridization intensity for that strain will be intimately correlated with the concentration of the compound (i.e. a specific strain).

Figure 6 illustrates an oligonucleotide comprising a lac operator flanked on each side by 40 nucleotides homologous to the promoter is the promoter which drives expression of the yabB yabC ftsL ftsI murE genes in an operon for use in inserting the lac operator into the promoter.

Figure 7 is an IPTG dose response curve in *E. coli* transformed with an IPTG-inducible plasmid containing either an antisense clone to the *E. coli* ribosomal protein *rplW* (AS-*rplW*) which is required for protein synthesis and essential for cell proliferation, or an antisense clone to the *elaD* (AS-*elaD*) gene which is not known to be involved in protein synthesis and which is also essential for proliferation.

Figure 8A is a tetracycline dose response curve in *E. coli* transformed with an IPTG-inducible plasmid containing antisense to *rplW* (AS-*rplW*) in the absence (0) or presence of IPTG at concentrations that result in 20% and 50% growth inhibition.

Figure 8B is a tetracycline dose response curve in *E. coli* transformed with an IPTG-inducible plasmid containing antisense to *elaD* (AS-*elaD*)in the absence (0) or presence of IPTG at concentrations that result in 20% and 50% growth inhibition.

Figure 9 is a graph showing the fold increase in tetracycline sensitivity of *E. coli* transfected with antisense clones to essential ribosomal proteins *L23* (AS-*rplW*) and *L7/L12* and *L10* (AS-*rplLrplJ*). Antisense clones to genes known to not be directly involved in protein synthesis, *atpB/E* (AS-*atpB/E*), *visC* (AS-*visC*), *elaD* (AS-*elaD*), *yohH* (AS-*yohH*), are much less sensitive to tetracycline.

Figure 10 illustrates the results of an assay in which *Staphylococcus aureus* cells transcribing an antisense nucleic acid complementary to the *gyrB* gene encoding the β subunit of gyrase were contacted with several antibiotics whose targets were known.

Figure 11 illustrates a microtitration plate which contains antibiotic and inducer at gradient concentrations in a matrix format in 10 times excess quantity.

Figure 12 illustrates the results of an experiment demonstrating that at appropriate concentrations of inducer, cells which overexpress the *defB* gene product were able to grow at elevated concentrations of the antibiotic actinonin

Figure 13 illustrates the results of an experiment demonstrating that at appropriate concentrations of inducer cells which overexpress the *folA* gene product were able to grow at elevated concentrations of the antibiotic trimethoprim.

Figure 14 illustrates the results of an experiment demonstrating that overexpression of the *fabI* gene confers resistance to triclosan, which acts on the gene product of the *fabI* gene, but does not confer resistance to cerulenin, trimethoprim, or actinonin, each of which act on other gene products.

Figure 15 illustrates the results of an experiment demonstrating that overexpression of the *folA* gene confers resistance to trimethoprim, which acts on the gene product of the *folA* gene but does not confer resistance to triclosan, cerulenin, or actinonin, each of which act on other gene products.

Figure 16 illustrates the results of an experiment demonstrating that overexpression of the *defB* gene conferred resistance to actinonin, which acts on the gene product of the *defB* gene but

does not confer resistance to cerulenin, trimethoprim, or triclosan, each of which act on other gene products.

Figure 17 illustrates the results of an experiment demonstrating that overexpression of the *fabF* gene conferred resistance to cerulenin, which acts on the gene product of the *fabF* gene, β

5   keto-acyl carrier protein synthase but does not confer resistance to triclosan, trimethoprim, or actinonin, each of which act on other gene products.

Figure 18 illustrates the results of experiments in which a mixture of nine strains was grown wells in a 96 well plate in medium containing various concentrations of inducer and a sufficient concentration of actinonin, cerulenin, triclosan or trimethoprim to inhibit the growth of

10   strains which do not overexpress the targets of these antibiotics.

Detailed Description of Embodiments of the Invention

The present invention describes a group of prokaryotic genes and gene families required for cellular proliferation. Exemplary genes and gene families from *Escherichia coli, Staphylococcus aureus, Enterococcus faecalis, Klebsiella pneumoniae, Pseudomonas aeruginosa, Salmonella*

15   *typhimurium, Acinetobacter baumannii, Bacillus anthracis, Bacteroides fragilis, Bordetella pertussis, Borrelia burgdorferi, Burkholderia cepacia, Burkholderia fungorum, Burkholderia mallei, Campylobacter jejuni, Chlamydia pneumoniae, Chlamydia trachomatis, Clostridium acetobutylicum, Clostridium botulinum, Clostridium difficile, Corynebacterium diptheriae, Enterobacter cloacae, Enterococcus faecium, Haemophilus influenzae, Helicobacter pylori,*

20   *Legionella pneumophila, Listeria monocytogenes, Moraxella catarrhalis, Mycobacterium avium, Mycobacterium bovis, Mycobacterium leprae, Mycobacterium tuberculosis, Mycoplasma genitalium, Mycoplasma pneumoniae, Neisseria gonorrhoeae, Neisseria meningitidis, Pasteurella multocida, Proteus mirabilis, Pseudomonas putida, Pseudomonas syringae, Salmonella paratyphi, Salmonella typhi, Staphylococcus epidermidis, Staphylococcus haemolyticus, Streptococcus*

25   *mutans, Streptococcus pneumoniae, Streptococcus pyogenes, Treponema pallidum, Ureaplasma urealyticum, Vibrio cholera* and *Yersinia pestis* are provided. A proliferation-required gene or gene family is one where, in the absence or substantial reduction of a gene transcript and/or gene product, growth or viability of the cell or microorganism is reduced or eliminated. Thus, as used herein, the terminology "proliferation-required" or "required for proliferation" encompasses instances where the

30   absence or substantial reduction of a gene transcript and/or gene product completely eliminates cell growth as well as instances where the absence of a gene transcript and/or gene product merely reduces cell growth. These proliferation-required genes can be used as potential targets for the generation of new antimicrobial agents. To achieve that goal, the present invention also encompasses assays for analyzing proliferation-required genes and for identifying compounds which interact with the gene

35   and/or gene products of the proliferation-required genes. In addition, the present invention contemplates the expression of genes and the purification of the proteins encoded by the nucleic acid sequences identified as required proliferation genes and reported herein. The purified proteins can be

used to generate reagents and screen small molecule libraries or other candidate compound libraries for compounds that can be further developed to yield novel antimicrobial compounds.

The present invention also describes methods for identification of nucleotide sequences homologous to these genes and polypeptides described herein, including nucleic acids comprising

5   nucleotide sequences homologous to the nucleic acids of SEQ ID NOS.: 6214-42397 and polypeptides homologous to the polypeptides of SEQ ID NOs.: 42398-78581. For example, these sequences may be used to identify homologous coding nucleic acids, homologous antisense nucleic acids, or homologous polypeptides in microorganisms such as *Acinetobacter baumannii, Anaplasma marginale, Aspergillus fumigatus, Bacillus anthracis, Bacteroides fragilis, Bordetella pertussis,*

10   *Borrelia burgdorferi, Burkholderia cepacia, Burkholderia fungorum, Burkholderia mallei, Campylobacter jejuni, Candida albicans, Candida glabrata* (also called *Torulopsis glabrata*), *Candida tropicalis, Candida parapsilosis, Candida guilliermondii, Candida krusei, Candida kefyr* (also called *Candida pseudotropicalis*), *Candida dubliniensis, Chlamydia pneumoniae, Chlamydia trachomatis, Clostridium acetobutylicum, Clostridium botulinum, Clostridium difficile, Clostridium*

15   *perfringens, Coccidioides immitis, Corynebacterium diptheriae, Cryptococcus neoformans, Enterobacter cloacae, Enterococcus faecalis, Enterococcus faecium, Escherichia coli, Haemophilus influenzae, Helicobacter pylori, Histoplasma capsulatum, Klebsiella pneumoniae, Legionella pneumophila, Listeria monocytogenes, Moraxella catarrhalis, Mycobacterium avium, Mycobacterium bovis, Mycobacterium leprae, Mycobacterium tuberculosis, Mycoplasma*

20   *genitalium, Mycoplasma pneumoniae, Neisseria gonorrhoeae, Neisseria meningitidis, Nocardia asteroides, Pasteurella haemolytica, Pasteurella multocida, Pneumocystis carinii, Proteus mirabilis, Proteus vulgaris, Pseudomonas aeruginosa, Pseudomonas putida, Pseudomonas syringae, Salmonella bongori, Salmonella cholerasuis, Salmonella enterica, Salmonella paratyphi, Salmonella typhi, Salmonella typhimurium, Shigella boydii, Shigella dysenteriae, Shigella flexneri,*

25   *Shigella sonnei, Staphylococcus aureus, Staphylococcus epidermidis, Staphylococcus haemolyticus, Streptococcus pneumoniae, Streptococcus mutans, Streptococcus pyogenes, Treponema pallidum, Ureaplasma urealyticum, Vibrio cholerae, Vibrio parahaemolyticus, Vibrio vulnificans, Yersinia enterocolitica, Yersinia pestis* or any species falling within the genera of any of the above species. In some embodiments, the homologous coding nucleic acids, homologus antisense nucleic acids, or

30   homologous polypeptides are identified in an organism other than *E. coli.*

The homologous coding nucleic acids, homologous antisense nucleic acids, or homologous polypeptides, may then be used in each of the methods described herein, including methods of identifying compounds which inhibit the proliferation of the organism containing the homologous coding nucleic acid, homologous antisense nucleic acid or homologous polypeptide, methods of

35   inhibiting the growth of the organism containing the homologous coding nucleic acid, homologus antisense nucleic acid or homologous polypeptide, methods of identifying compounds which influence the activity or level of a gene product required for proliferation of the organism containing the homologous coding nucleic acid, homologous antisense nucleic acid or homologous

polypeptide, methods for identifying compounds or nucleic acids having the ability to reduce the level or activity of a gene product required for proliferation of the organism containing the homologous coding nucleic acid, homologous antisense nucleic acid or homologous polypeptide, methods of inhibiting the activity or expression of a gene in an operon required for proliferation of

5   the organism containing the homologous coding nucleic acid, homologous antisense nucleic acid or homologous polypeptide, methods for identifying a gene required for proliferation of the organism containing the homologous coding nucleic acid, homologous antisense nucleic acid or homologous polypeptide, methods for identifying the biological pathway in which a gene or gene product required for proliferation of the organism containing the homologous coding nucleic acid,

10   homologous antisense nucleic acid or homologous polypeptide lies, methods for identifying compounds having activity against biological pathway required for proliferation of the organism containing the homologous coding nucleic acid, homologous antisense nucleic acid or homologous polypeptide, methods for determining the biological pathway on which a test compound acts in the organism containing the homologous coding nucleic acid, homologous antisense nucleic acid or

15   homologous polypeptide, methods of replacing an endogenous promoter with a regulatable promoter which controls the expression of the homologous coding nucleic acid, homologous antisense nucleic acid or homologous polypeptide, methods of inserting an operator within or near an endogenous promoter to provide regulatable expression of the homologous coding nucleic acid, homologous antisense nucleic acid or homologous polypeptide, methods of identifying the target on

20   which a compound acts in the organism containing the homologous coding nucleic acid, homologous antisense nucleic acid or homologous polypeptide, and methods of inhibiting the proliferation of the organism containing the homologous coding nucleic acid, homologous antisense nucleic acid or homologous polypeptide in a subject. In some embodiments of the present invention, the methods are performed using an organism, other than *E. coli* or a gene or gene

25   product from an organism other than *E. coli*.

One embodiment of the present invention utilizes a novel method to identify proliferation-required sequences. Generally, a library of nucleic acid sequences from a given source are subcloned or otherwise inserted immediately downstream of an inducible promoter on an appropriate vector, such as a *Staphylococcus aureus/E. coli* or *Pseudomonas aeruginosa/ E. coli* shuttle vector, or a vector

30   which will replicate in both *Salmonella typhimurium* and *Klebsiella pneumoniae,* or other vector or shuttle vector capable of functioning in the intended organism, thus forming an expression library. It is generally preferred that expression is directed by a regulatable promoter sequence such that expression level can be adjusted by addition of variable concentrations of an inducer molecule or of an inhibitor molecule to the medium. For example, a number of regulatable promoters useful for regulating the

35   expression of nucleic acid sequences over a wide range of expression levels are described in U.S. Patent Application Serial Number 10/032,393, filed December 21, 2001. Temperature activated promoters, such as promoters regulated by temperature sensitive repressors, such as the lambda C_{I857} repressor, are also envisioned. Although the insert nucleic acids may be derived from the chromosome

of the cell or microorganism into which the expression vector is to be introduced, because the insert is not in its natural chromosomal location, the insert nucleic acid is an exogenous nucleic acid for the purposes of the discussion herein. The term "expression" is defined as the production of a sense or antisense RNA molecule from a gene, gene fragment, genomic fragment, chromosome, operon or

5   portion thereof. Expression can also be used to refer to the process of peptide or polypeptide synthesis. An expression vector is defined as a vehicle by which a ribonucleic acid (RNA) sequence is transcribed from a nucleic acid sequence carried within the expression vehicle. The expression vector can also contain features that permit translation of a protein product from the transcribed RNA message expressed from the exogenous nucleic acid sequence carried by the expression vector. Accordingly, an

10   expression vector can produce an RNA molecule as its sole product or the expression vector can produce a RNA molecule that is ultimately translated into a protein product.

Once generated, the expression library containing the exogenous nucleic acid sequences is introduced into a population of cells (such as the organism from which the exogenous nucleic acid sequences were obtained) to search for genes that are required for bacterial proliferation. Because the

15   library molecules are foreign, in context, to the population of cells, the expression vectors and the nucleic acid segments contained therein are considered exogenous nucleic acid.

Expression of the exogenous nucleic acid fragments in the test population of cells containing the expression library is then activated. Activation of the expression vectors consists of subjecting the cells containing the vectors to conditions that result in the expression of the exogenous nucleic acid

20   sequences carried by the expression library. The test population of cells is then assayed to determine the effect of expressing the exogenous nucleic acid fragments on the test population of cells. Those expression vectors that negatively impact the growth of the cells upon induction of expression of the random sequences contained therein are identified, isolated, and purified for further study.

In some embodiments, vectors which comprises a regulatable fusion promoter selected

25   from a suite of fusion promoters, wherein the promoter suite is useful for modulating both the basal and maximal levels of transcription of a nucleic acid over a wide dynamic range thus allowing the desired level of production of a transcript, can be used to express exogenous nucleic acids, including the nucleic acids of the present invention. Such promoters are described in U.S. Patent Application Serial Number 10/032,393, filed December 21, 2001, the disclosure of which is

30   incorported herein by reference in its entirety.

In some other embodiments, vectors useful for the production of stabilized mRNA having an increased lifetime (including antisense RNA) in Gram negative organisms are described in U.S. Provisional Patent Application Serial Number 60/343,512, filed December 21, 2001. Briefly, the stabilized antisense RNA may comprise an antisense RNA which was identified as inhibiting

35   proliferation as described above which has been engineered to contain at least one stem loop flanking each end of the antisense nucleic acid. In some embodiments, the at least one stem-loop structure formed at the 5' end of the stabilized antisense nucleic acid comprises a flush, double stranded 5' end. In some embodiments, one or more of the stem loops comprises a rho independent

terminator. In additional embodiments, the stabilized antisense RNA lacks a ribosome binding site. In further embodiments, the stabilized RNA lacks sites which are cleaved by one or more RNAses, such as RNAse E or RNAse III. In some embodiments, the stabilized antisense RNA may be transcribed in a cell which the activity of at least one enzyme involved in RNA degradation has

5   been reduced. For example, the activity of an enzyme such as RNase E, RNase II, RNase III, polynucleotide phosphorylase, and poly(A) polymerase, RNA helicase, enolase or an enzyme having similar functions may be reduced in the cell.

Alternatively, genes required for proliferation may be identified by replacing the natural promoter for the proliferation required gene with a regulatable promoter as described above. The

10   growth of such strains under conditions in which the promoter is active or non-repressed is compared to the growth under conditions in which the promoter is inactive or repressed. If the strains fail to grow or grow at a substantially reduced rate under conditions in which the promoter is inactive or repressed but grow normally under conditions in which the promoter is active or non-repressed, then the gene which is operably linked to the regulatable promoter encodes a gene

15   product required for proliferation. For example, proliferation-required genes and gene products identified using promoter replacement are described in U.S. Patent Application Serial Number 09/948,993.

For example, in some embodiments, the natural promoter may be replaced using techniques which employ homologous recombination to exchange a promoter present on the chromosome of

20   the cell with the desired promoter. In such methodology, a nucleic acid comprising a promoter replacement cassette is introduced into the cell. As illustrated in Figure 1A, the promoter replacement cassette comprises a 5' region homologous to the sequence which is 5' of the natural promoter in the chromosome, the promoter which is to replace the chromosomal promoter and a 3' region which is homologous to sequences 3' of the natural promoter in the chromosome. In some

25   embodiments, the promoter replacement cassette may also include a nucleic acid encoding an identifiable or selectable marker disposed between the 5' region which is homologous to the sequence 5' of the natural promoter and the promoter which is to replace the chromosomal promoter. If desired, the promoter replacement cassette may also contain a transcriptional terminator 3' of the gene encoding an identifiable or selectable marker, as illustrated in Figure 1B.

30   As illustrated in Figure 1A and 1B, homologous recombination is allowed to occur between the chromosomal region containing the natural promoter and the promoter replacement cassette. Cells in which the promoter replacement cassette has integrated into the chromosome are identified or selected. To confirm that homologous recombination has occurred, the chromosomal structure of the cells may be verified by Southern analysis or PCR.

35   In some embodiments, the promoter replacement cassette may be introduced into the cell as a linear nucleic acid, such a PCR product or a restriction fragment. Alternatively, the promoter replacement may be introduced into the cell on a plasmid. Figures 1A and 1B illustrates the

replacement of a chromosomal promoter with a desired promoter through homologous recombination.

In some embodiments, the cell into which the promoter replacement cassette is introduced may carry mutations which enhance its ability to be transformed with linear DNA or which enhance
5   the frequency of homologous recombination. For example, if the cell is an *Escherichia coli* cell it may have a mutation in the gene encoding Exonuclease V of the RecBCD recombination complex. If the cell is an *Escherichia coli* cell it may have a mutation that activates the RecET recombinase of the Rac prophage and/or a mutation that enhances recombination through the RecF pathway. For example, the *Escherichia coli* cells may be RecB or RecC mutants carrying an sbcA or sbcB
10   mutation. Alternatively, the *Escherichia coli* cells may be recD mutants. In other embodiments the *Escherichia coli* cells may express the λ Red recombination genes. For example, *Escherichia coli* cells suitable for use in techniques employing homologous recombination have been described in Datsenko, K.A. and Wanner, B.L., PNAS 97:6640-6645 (2000); Murphy, K.C., J. Bact 180: 2053-2071 (1998); Zhang, Y., et al., Nature Genetics 20: 123-128 (1998); and Muyrers, J.P.P. et al.,
15   Genes & Development 14: 1971-1982 (2000). It will be appreciated that cells carrying mutations in similar genes may be constructed in organisms other than *Escherichia coli*.

In some embodiments of the present invention, a regulatable fusion promoter selected from a suite of fusion promoters, wherein the promoter suite is useful for modulating both the basal and maximal levels of transcription of a nucleic acid over a wide dynamic range thus allowing the
20   desired level of production of a transcript, is with the promoter replacement methods described above. Such promoters are described in U.S. Patent Application Serial Number 10/032,393, filed December 21, 2001, the disclosure of which is incorported herein by reference in its entirety.

A variety of assays are contemplated to identify nucleic acid sequences that negatively impact growth upon expression. In one embodiment, growth in cultures expressing exogenous nucleic acid
25   sequences and growth in cultures not expressing these sequences is compared. Growth measurements are assayed by examining the extent of growth by measuring optical densities. Alternatively, enzymatic assays can be used to measure bacterial growth rates to identify exogenous nucleic acid sequences of interest. Colony size, colony morphology, and cell morphology are additional factors used to evaluate growth of the host cells. Those cultures that fail to grow or grow at a reduced rate
30   under expression conditions are identified as containing an expression vector encoding a nucleic acid fragment that negatively affects a proliferation-required gene.

Once exogenous nucleic acids of interest are identified, they are analyzed. The first step of the analysis is to acquire the nucleotide sequence of the nucleic acid fragment of interest. To achieve this end, the insert in those expression vectors identified as containing a nucleotide sequence of interest is
35   sequenced, using standard techniques well known in the art. The next step of the process is to determine the source of the nucleotide sequence. As used herein "source" means the genomic region containing the cloned fragment.

Determination of the gene(s) corresponding to the nucleotide sequence is achieved by comparing the obtained sequence data with databases containing known protein and nucleotide sequences from various microorganisms. Thus, initial gene identification is made on the basis of significant sequence similarity or identity to either characterized or predicted *Escherichia coli,*
5   *Staphylococcus aureus, Enterococcus faecalis, Klebsiella pneumoniae, Pseudomonas aeruginosa,* and *Salmonella typhimurium* genes or their encoded proteins and/or homologues in other species.

The number of nucleotide and protein sequences available in database systems has been growing exponentially for years. For example, the complete nucleotide sequences of *Caenorhabditis elegans* and several bacterial genomes, including *E. coli, Aeropyrum pernix, Aquifex aeolicus,*
10   *Archaeoglobus fulgidus, Bacillus subtilis, Borrelia burgdorferi, Chlamydia pneumoniae, Chlamydia trachomatis, Clostridium tetani, Corynebacterium diptheria, Deinococcus radiodurans, Haemophilus influenzae, Helicobacter pylori 26695, Helicobacter pylori J99, Methanobacterium thermoautotrophicum, Methanococcus jannaschii, Mycobacterium tuberculosis,   Mycoplasma genitalium, Mycoplasma pneumoniae, Pseudomonas aeruginosa, Pyrococcus abyssi, Pyrococcus*
15   *horikoshii, Rickettsia prowazekii, Synechocystis PCC6803, Thermotoga maritima, Treponema pallidum, Bordetella pertussis, Campylobacter jejuni, Clostridium acetobutylicum, Mycobacterium tuberculosis CSU#93, Neisseria gonorrhoeae, Neisseria meningitidis, Pseudomonas aeruginosa, Pyrobaculum aerophilum, Pyrococcus furiosus, Rhodobacter capsulatus, Salmonella typhimurium, Streptococcus mutans, Streptococcus pyogenes, Ureaplasma urealyticum* and *Vibrio cholera* are
20   available. This nucleotide sequence information is stored in a number of databanks, such as GenBank, the National Center for Biotechnology Information (NCBI), the Genome Sequencing Center (http://genome.wustl.edu/gsc/salmonella.shtml),   and   the   Sanger   Centre (http://www.sanger.ac.uk/projects/S___typhi) which are publicly available for searching.   A variety of computer programs are available to assist in the analysis of the sequences stored within these
25   databases.   FASTA, (W. R. Pearson (1990) "Rapid and Sensitive Sequence Comparison with FASTP and FASTA" Methods in Enzymology 183:63- 98), Sequence Retrieval System (SRS), (Etzold & Argos, SRS an indexing and retrieval tool for flat file data libraries. Comput. Appl. Biosci. 9:49-57, 1993) are two examples of computer programs that can be used to analyze sequences of interest. In one embodiment of the present invention, the BLAST family of computer
30   programs, which includes BLASTN version 2.0 with the default parameters, or BLASTX version 2.0 with the default parameters, is used to analyze nucleotide sequences.

BLAST, an acronym for "Basic Local Alignment Search Tool," is a family of programs for database similarity searching. The BLAST family of programs includes: BLASTN, a nucleotide sequence database searching program, BLASTX, a protein database searching program where the input
35   is a nucleic acid sequence; and BLASTP, a protein database searching program. BLAST programs embody a fast algorithm for sequence matching, rigorous statistical methods for judging the significance of matches, and various options for tailoring the program for special situations. Assistance

in using the program can be obtained by e-mail at blast@ncbi.nlm.nih.gov. tBLASTX can be used to translate a nucleotide sequence in all three potential reading frames into an amino acid sequence.

Bacterial genes are often transcribed in polycistronic groups. These groups comprise operons, which are a collection of genes and intergenic sequences under common regulation. The genes of an
5   operon are transcribed on the same mRNA and are often related functionally. Given the nature of the screening protocol, it is possible that the identified exogenous nucleic acid corresponds to a gene or portion thereof with or without adjacent noncoding sequences, an intragenic sequence (i.e. a sequence within a gene), an intergenic sequence (i.e. a sequence between genes), a nucleotide sequence spanning at least a portion of two or more genes, a 5' noncoding region or a 3' noncoding region located
10   upstream or downstream from the actual nucleotide sequence that is required for bacterial proliferation. Accordingly, it is often desirable to determine which gene(s) that is encoded within the operon is individually required for proliferation.

In one embodiment of the present invention, an operon is identified and then dissected to determine which gene or genes are required for proliferation. Operons can be identified by a
15   variety of means known to those in the art. For example, the RegulonDB DataBase described by Huerta et al. (*Nucl. Acids Res.* 26:55-59, 1998), which may also be found on the website http://www.cifn.unam.mx/Computational_Biology/regulondb/, provides information about operons in *Escherichia coli*. The Subtilist database (http://bioweb.pasteur.fr/GenoList/SubtiList), (Moszer, I., Glaser, P. and Danchin, A. (1995) Microbiology 141: 261-268 and Moszer, I (1998) FEBS
20   Letters 430: 28-36, may also be used to predict operons. This database lists genes from the fully sequenced, Gram positive bacteria, *Bacillus subtilis*, together with predicted promoters and terminator sites. This information can be used in conjunction with the *Staphylococcus aureus* genomic sequence data to predict operons and thus produce a list of the genes affected by the antisense nucleic acids of the present invention. The *Pseudomonas aeruginosa* web site
25   (http://www.pseudomonas.com) can be used to help predict operon organization in this bacterium. The   databases   available   from   the   Genome   Sequencing   Center (http://genome.wustl.edu/gsc/salmonella.shtml),   and   the   Sanger   Centre (http://www.sanger.ac.uk/projects/S___typhi) may be used to predict operons in *Salmonella typhimurium*. The TIGR microbial database has an incomplete version of the *E. faecalis* genome
30   http://www.tigr.org/cgi-bin/BlastSearch/blast.cgi?organism=e_faecalis. One can take a nucleotide sequence and BLAST it for homologs.

A number of techniques that are well known in the art can be used to dissect the operon. Analysis of RNA transcripts by Northern blot or primer extension techniques are commonly used to analyze operon transcripts. In one aspect of this embodiment, gene disruption by homologous
35   recombination is used to individually inactivate the genes of an operon that is thought to contain a gene required for proliferation.

Several gene disruption techniques have been described for the replacement of a functional gene with a mutated, non-functional (null) allele. These techniques generally involve the use of

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homologous recombination. One technique using homologous recombination in *Staphylococcus aureus* is described in Xia et a.. 1999, Plasmid 42: 144-149. This technique uses crossover PCR to create a null allele with an in-frame deletion of the coding region of a target gene. The null allele is constructed in such a way that nucleotide sequences adjacent to the wild type gene are retained.

5   These homologous sequences surrounding the deletion null allele provide targets for homologous recombination so that the wild type gene on the *Staphylococcus aureus* chromosome can be replaced by the constructed null allele. This method can be used with other bacteria as well, including *Salmonella* and *Klebsiella* species. Similar gene disruption methods that employ the counter selectable marker *sacB* (Schweizer, H. P., Klassen, T. and Hoang, T. (1996) Mol. Biol. of

10   *Pseudomonas*. ASM press, 229-237, are available for *Pseudomonas, Salmonella* and *Klebsiella* species. *E. faecalis* genes can be disrupted by recombining in a non-replicating plasmid that contains an internal fragment to that gene (Leboeuf, C., L. Leblanc, Y. Auffray and A. Hartke. 2000. J. Bacteriol. 182:5799-5806.

       The crossover PCR amplification product is subcloned into a suitable vector having a

15   selectable marker, such as a drug resistance marker. In some embodiments the vector may have an origin of replication which is functional in *E. coli* or another organism distinct from the organism in which homologous recombination is to occur, allowing the plasmid to be grown in *E. coli* or the organism other than that in which homologous recombination is to occur, but may lack an origin of replication functional in *Escherichia coli, Staphylococcus aureus, Enterococcus faecalis, Klebsiella*

20   *pneumoniae, Pseudomonas aeruginosa, Salmonella typhimurium, Acinetobacter baumannii, Bacillus anthracis, Bacteroides fragilis, Bordetella pertussis, Borrelia burgdorferi, Burkholderia cepacia, Burkholderia fungorum, Burkholderia mallei, Campylobacter jejuni, Chlamydia pneumoniae, Chlamydia trachomatis, Clostridium acetobutylicum, Clostridium botulinum, Clostridium difficile, Corynebacterium diptheriae, Enterobacter cloacae, Enterococcus faecium,*

25   *Haemophilus influenzae, Helicobacter pylori, Legionella pneumophila, Listeria monocytogenes, Moraxella catarrhalis, Mycobacterium avium, Mycobacterium bovis, Mycobacterium leprae, Mycobacterium tuberculosis, Mycoplasma genitalium, Mycoplasma pneumoniae, Neisseria gonorrhoeae, Neisseria meningitidis, Pasteurella multocida, Proteus mirabilis, Pseudomonas putida, Pseudomonas syringae, Salmonella paratyphi, Salmonella typhi, Staphylococcus*

30   *epidermidis, Staphylococcus haemolyticus, Streptococcus mutans, Streptococcus pneumoniae, Streptococcus pyogenes, Treponema pallidum, Ureaplasma urealyticum, Vibrio cholerae* or *Yersinia pestis* such that selection of the selectable marker requires integration of the vector into the homologous region of the *Escherichia coli, Staphylococcus aureus, Enterococcus faecalis, Klebsiella pneumoniae, Pseudomonas aeruginosa, Salmonella typhimurium, Acinetobacter*

35   *baumannii, Bacillus anthracis, Bacteroides fragilis, Bordetella pertussis, Borrelia burgdorferi, Burkholderia cepacia, Burkholderia fungorum, Burkholderia mallei, Campylobacter jejuni, Chlamydia pneumoniae, Chlamydia trachomatis, Clostridium acetobutylicum, Clostridium botulinum, Clostridium difficile, Corynebacterium diptheriae, Enterobacter cloacae, Enterococcus*

faecium, Haemophilus influenzae, Helicobacter pylori, Legionella pneumophila, Listeria monocytogenes, Moraxella catarrhalis, Mycobacterium avium, Mycobacterium bovis, Mycobacterium leprae, Mycobacterium tuberculosis, Mycoplasma genitalium, Mycoplasma pneumoniae, Neisseria gonorrhoeae, Neisseria meningitidis, Pasteurella multocida, Proteus

5   *mirabilis, Pseudomonas putida, Pseudomonas syringae, Salmonella paratyphi, Salmonella typhi, Staphylococcus epidermidis, Staphylococcus haemolyticus, Streptococcus mutans, Streptococcus pneumoniae, Streptococcus pyogenes, Treponema pallidum, Ureaplasma urealyticum, Vibrio cholerae* or *Yersinia pestis* chromosome. Usually a single crossover event is responsible for this integration event such that the *Escherichia coli, Staphylococcus aureus, Enterococcus faecalis,*

10   *Klebsiella pneumoniae, Pseudomonas aeruginosa, Salmonella typhimurium, Acinetobacter baumannii, Bacillus anthracis, Bacteroides fragilis, Bordetella pertussis, Borrelia burgdorferi, Burkholderia cepacia, Burkholderia fungorum, Burkholderia mallei, Campylobacter jejuni, Chlamydia pneumoniae, Chlamydia trachomatis, Clostridium acetobutylicum, Clostridium botulinum, Clostridium difficile, Corynebacterium diptheriae, Enterobacter cloacae, Enterococcus*

15   *faecium, Haemophilus influenzae, Helicobacter pylori, Legionella pneumophila, Listeria monocytogenes, Moraxella catarrhalis, Mycobacterium avium, Mycobacterium bovis, Mycobacterium leprae, Mycobacterium tuberculosis, Mycoplasma genitalium, Mycoplasma pneumoniae, Neisseria gonorrhoeae, Neisseria meningitidis, Pasteurella multocida, Proteus mirabilis, Pseudomonas putida, Pseudomonas syringae, Salmonella paratyphi, Salmonella typhi,*

20   *Staphylococcus epidermidis, Staphylococcus haemolyticus, Streptococcus mutans, Streptococcus pneumoniae, Streptococcus pyogenes, Treponema pallidum, Ureaplasma urealyticum, Vibrio cholera* or *Yersinia pestis* chromosome now contains a tandem duplication of the target gene consisting of one wild type allele and one deletion null allele separated by vector sequence. Subsequent resolution of the duplication results in both removal of the vector sequence and either

25   restoration of the wild type gene or replacement by the in-frame deletion. The latter outcome will not occur if the gene should prove essential. A more detailed description of this method is provided in Example 10 below. It will be appreciated that this method may be practiced with any of the nucleic acids or organisms described herein.

Recombinant DNA techniques can be used to express the entire coding sequences of the gene

30   identified as required for proliferation, or portions thereof. The over-expressed proteins can be used as reagents for further study. The identified exogenous sequences are isolated, purified, and cloned into a suitable expression vector using methods well known in the art. If desired, the nucleic acids can contain the nucleotide sequences encoding a signal peptide to facilitate secretion of the expressed protein.

35   Expression of fragments of the bacterial genes identified as required for proliferation is also contemplated by the present invention. The fragments of the identified genes can encode a polypeptide comprising at least 5, at least 10, at least 15, at least 20, at least 25, at least 30, at least 35, at least 40, at least 45, at least 50, at least 55, at least 60, at least 65, at least 75, or more than 75 consecutive amino

acids of a gene complementary to one of the identified sequences of the present invention. The nucleic acids inserted into the expression vectors can also contain endogenous sequences upstream and downstream of the coding sequence.

When expressing the encoded protein of the identified nucleic acid required for bacterial
5   proliferation or a fragment thereof, the nucleic acid to be expressed is operably linked to a promoter in an expression vector using conventional cloning technology. The expression vector can be any of the bacterial, insect, yeast, or mammalian expression systems known in the art. Commercially available vectors and expression systems are available from a variety of suppliers including Genetics Institute (Cambridge, MA), Stratagene (La Jolla, California), Promega (Madison, Wisconsin), and Invitrogen
10   (San Diego, California). If desired, to enhance expression and facilitate proper protein folding, the codon usage and codon bias of the sequence can be optimized for the particular expression organism in which the expression vector is introduced, as explained by Hatfield, et al., U.S. Patent No. 5,082,767, incorporated herein by this reference. Fusion protein expression systems are also contemplated by the present invention.

15   Following expression of the protein encoded by the identified exogenous nucleic acid, the protein may be purified. Protein purification techniques are well known in the art. Proteins encoded and expressed from identified exogenous nucleic acids can be partially purified using precipitation techniques, such as precipitation with polyethylene glycol. Alternatively, epitope tagging of the protein can be used to allow simple one step purification of the protein. In addition, chromatographic methods
20   such as ion-exchange chromatography, gel filtration, use of hydroxyapaptite columns, immobilized reactive dyes, chromatofocusing, and use of high-performance liquid chromatography, may also be used to purify the protein. Electrophoretic methods such as one-dimensional gel electrophoresis, high-resolution two-dimensional polyacrylamide electrophoresis, isoelectric focusing, and others are contemplated as purification methods. Also, affinity chromatographic methods, comprising antibody
25   columns, ligand presenting columns and other affinity chromatographic matrices are contemplated as purification methods in the present invention.

The purified proteins produced from the gene encoding sequences identified as required for proliferation can be used in a variety of protocols to generate useful antimicrobial reagents. In one embodiment of the present invention, antibodies are generated against the proteins expressed from the
30   identified exogenous nucleic acids. Both monoclonal and polyclonal antibodies can be generated against the expressed proteins. Methods for generating monoclonal and polyclonal antibodies are well known in the art. Also, antibody fragment preparations prepared from the produced antibodies discussed above are contemplated.

In addition, the purified protein, fragments thereof, or derivatives thereof may be administered
35   to an individual in a pharmaceutically acceptable carrier to induce an immune response against the protein. Preferably, the immune response is a protective immune response which protects the individual. Methods for determining appropriate dosages of the protein and pharmaceutically acceptable carriers may be determined empiracally and are familiar to those skilled in the art.

Another application for the purified proteins of the present invention is to screen small molecule libraries for candidate compounds active against the various target proteins of the present invention. Advances in the field of combinatorial chemistry provide methods, well known in the art, to produce large numbers of candidate compounds that can have a binding, or otherwise inhibitory effect

5   on a target protein. Accordingly, the screening of small molecule libraries for compounds with binding affinity or inhibitory activity for a target protein produced from an identified gene is contemplated by the present invention.

In some embodiments of the present invention, a cell sensitized by expressing an an antisense nucleic acid comprising a nucleotide sequence selected from the group consisting of SEQ ID NOs.:

10   1-6213, an antisense nucleic acid comprising at least 10, 15, 20, 25, 30, 35, 40, 50, 75, 100, 150, 200, 300, 400, or 500 consecutive nucleotides of a nucleotide sequence selected from the group consisting of SEQ ID NOs.: 1-6213, a nucleic acid complementary to a nucleic acid comprising a nucleotide sequence selected from the group consisting of SEQ ID NOs.: 6214-42397, a nucleic acid complementary to a nucleic acid comprising at least 10, 15, 20, 25, 30, 35, 40, 50, 75, 100, 150,

15   200, 300, 400, or 500 consecutive nucleotides of a nucleotide sequence selected from the group consisting of SEQ ID NOs.: 6214-42397, a nucleic acid complementary to a nucleic acid which encodes a polypeptide comprising an amino acid sequence selected from the group consisting of SEQ ID NOs.: 42398-78581, a nucleic acid complementary to a nucleic acid which encodes at least 5, 10, 15, 20, 25, 30, 35, 40, 50, 75, 100, or 150 consecutive amino acids of a polypeptide sequence

20   selected from the group consisting of SEQ ID NOs.: 42398-78581, a homologous antisense nucleic acid, an antisense nucleic acid comprising at least 10, 15, 20, 25, 30, 35, 40, 50, 75, 100, 150, 200, 300, 400, or 500 consecutive nucleotides of a homologous nucleic acid, a nucleic acid complementary to a homologous coding nucleic acid, a nucleic acid complementary to at least 10, 15, 20, 25, 30, 35, 40, 50, 75, 100, 150, 200, 300, 400, or 500 consecutive nucleotides of a

25   homologous coding nucleic acid, a nucleic acid complementary to a nucleic acid which encodes a homologous polypeptide, or a nucleic acid complementary to a nucleic acid which encodes at least 5, 10, 15, 20, 25, 30, 35, 40, 50, 75, 100, or 150 consecutive amino acids of a homologous polypeptide, is contacted with one or more candidate compounds from a small molecule library. Candidate compounds which further inhibit the proliferation of the sensitized cell may be identified

30   as possessing inhibitory activity for a target protein or product produced by the gene to which the antisense sequence is complementary.

A number of vectors useful in the above methods are described in U.S. Patent Application Serial Number 10/032,393, filed December 21, 2001.

In some embodiments of the present invention, the methods for the production of stabilized

35   RNA, as described in U.S. Patent Application Serial Number 60/343,512, can be used for the production of a stabilized transcript, which corresponds to a nucleic acid described herein, having an increased lifetime in Gram-negative organisms. Briefly, the stabilized antisense RNA may comprise an antisense RNA which was identified as inhibiting proliferation as described above

which has been engineered to contain at least one stem loop flanking each end of the antisense nucleic acid. In some embodiments, the at least one stem-loop structure formed at the 5' end of the stabilized antisense nucleic acid comprises a flush, double stranded 5' end. In some embodiments, one or more of the stem loops comprises a rho independent terminator. In additional embodiments,

5　　the stabilized antisense RNA lacks a ribosome binding site. In further embodiments, the stabilized RNA lacks sites which are cleaved by one or more RNAses, such as RNAse E or RNAse III. In some embodiments, the stabilized antisense RNA may be transcribed in a cell which the activity of at least one enzyme involved in RNA degradation has been reduced. For example, the activity of an enzyme such as RNase E, RNase II, RNase III, polynucleotide phosphorylase, and poly(A)

10　　polymerase, RNA helicase, enolase or an enzyme having similar functions may be reduced in the cell.

The present invention further contemplates utility against a variety of other pathogenic microorganisms in addition to *Escherichia coli, Staphylococcus aureus, Enterococcus faecalis, Klebsiella pneumoniae, Pseudomonas aeruginosa, Salmonella typhimurium, Acinetobacter*

15　　*baumannii, Bacillus anthracis, Bacteroides fragilis, Bordetella pertussis, Borrelia burgdorferi, Burkholderia cepacia, Burkholderia fungorum, Burkholderia mallei, Campylobacter jejuni, Chlamydia pneumoniae, Chlamydia trachomatis, Clostridium acetobutylicum, Clostridium botulinum, Clostridium difficile, Corynebacterium diptheriae, Enterobacter cloacae, Enterococcus faecium, Haemophilus influenzae, Helicobacter pylori, Legionella pneumophila, Listeria*

20　　*monocytogenes, Moraxella catarrhalis, Mycobacterium avium, Mycobacterium bovis, Mycobacterium leprae, Mycobacterium tuberculosis, Mycoplasma genitalium, Mycoplasma pneumoniae, Neisseria gonorrhoeae, Neisseria meningitidis, Pasteurella multocida, Proteus mirabilis, Pseudomonas putida, Pseudomonas syringae, Salmonella paratyphi, Salmonella typhi, Staphylococcus epidermidis, Staphylococcus haemolyticus, Streptococcus mutans, Streptococcus*

25　　*pneumoniae, Streptococcus pyogenes, Treponema pallidum, Ureaplasma urealyticum, Vibrio cholerae* and *Yersinia pestis*. For example, homologous coding nucleic acids, homologous antisense nucleic acids or homologous polypeptides from other pathogenic microorganisms (including nucleic acids homologous to the nucleic acids of SEQ ID NOs.: 6214-42397, nucleic acids homologous to the antisense nucleic acids of SEQ ID NOs.: 1-6213, and polypeptides homologous to the

30　　polypeptides of SEQ ID NOs.: 42398-78581) may be identified using methods such as those described herein. The homologous coding nucleic acids, homologous antisense nucleic acids or homologous polypeptides may be used to identify compounds which inhibit the proliferation of these other pathogenic microorganisms using methods such as those described herein.

For example, the proliferation-required nucleic acids, antisense nucleic acids, and

35　　polypeptides from *Escherichia coli, Staphylococcus aureus, Enterococcus faecalis, Klebsiella pneumoniae, Pseudomonas aeruginosa, Salmonella typhimurium, Acinetobacter baumannii, Bacillus anthracis, Bacteroides fragilis, Bordetella pertussis, Borrelia burgdorferi, Burkholderia cepacia, Burkholderia fungorum, Burkholderia mallei, Campylobacter jejuni, Chlamydia*

pneumoniae, Chlamydia trachomatis, Clostridium acetobutylicum, Clostridium botulinum, Clostridium difficile, Corynebacterium diptheriae, Enterobacter cloacae, Enterococcus faecium, Haemophilus influenzae, Helicobacter pylori, Legionella pneumophila, Listeria monocytogenes, Moraxella catarrhalis, Mycobacterium avium, Mycobacterium bovis, Mycobacterium leprae,

5   *Mycobacterium tuberculosis, Mycoplasma genitalium, Mycoplasma pneumoniae, Neisseria gonorrhoeae, Neisseria meningitidis, Pasteurella multocida, Proteus mirabilis, Pseudomonas putida, Pseudomonas syringae, Salmonella paratyphi, Salmonella typhi, Staphylococcus epidermidis, Staphylococcus haemolyticus, Streptococcus mutans, Streptococcus pneumoniae, Streptococcus pyogenes, Treponema pallidum, Ureaplasma urealyticum, Vibrio cholerae* or

10   *Yersinia pestis* described herein (including the nucleic acids of SEQ ID NOs.: 6214-42397, the antisense nucleic acids of SEQ ID NOs: 1-6213, and the polypeptides of SEQ ID NOs.: 42398-78581) may be used to identify homologous coding nucleic acids, homologous antisense nucleic acids or homologous polypeptides required for proliferation in prokaryotes and eukaryotes. For example, nucleic acids or polypeptides required for the proliferation of protists, such as *Plasmodium* spp.;

15   plants; animals, such as *Entamoeba* spp. *and Contracaecum* spp; and fungi including *Candida* spp., (e.g., *Candida albicans*), *Cryptococcus neoformans*, and *Aspergillus fumigatus* may be identified. In one embodiment of the present invention, monera, specifically bacteria, including both Gram positive and Gram negative bacteria, are probed in search of novel gene sequences required for proliferation. Likewise, homologous antisense nucleic acids which may be used to inhibit growth of these organisms.

20   or to identify antibiotics may also be identified. These embodiments are particularly important given the rise of drug resistant bacteria.

     The number of bacterial species that are becoming resistant to existing antibiotics is growing. A partial list of these microorganisms includes: *Escherichia* spp., such as *E. coli, Enterococcus* spp, such as *E. faecalis; Pseudomonas* spp., *such as P. aeruginosa, Clostridium* spp., such as *C.*

25   *botulinum, Haemophilus* spp., such as *H. influenzae, Enterobacter* spp., such as *E. cloacae, Vibrio* spp., such as *V. cholera; Moraxala* spp., such as *M. catarrhalis; Streptococcus* spp., such as *S. pneumoniae, Neisseria* spp., such as *N. gonorrhoeae; Mycoplasma* spp., such as *Mycoplasma pneumoniae; Salmonella typhimurium; Helicobacter pylori; Escherichia coli;* and *Mycobacterium tuberculosis*. The genes and polypeptides identified as required for the proliferation of *Escherichia*

30   *coli, Staphylococcus aureus, Enterococcus faecalis, Klebsiella pneumoniae, Pseudomonas aeruginosa, Salmonella typhimurium, Acinetobacter baumannii, Bacillus anthracis, Bacteroides fragilis, Bordetella pertussis, Borrelia burgdorferi, Burkholderia cepacia, Burkholderia fungorum, Burkholderia mallei, Campylobacter jejuni, Chlamydia pneumoniae, Chlamydia trachomatis, Clostridium acetobutylicum, Clostridium botulinum, Clostridium difficile, Corynebacterium*

35   *diptheriae, Enterobacter cloacae, Enterococcus faecium, Haemophilus influenzae, Helicobacter pylori, Legionella pneumophila, Listeria monocytogenes, Moraxella catarrhalis, Mycobacterium avium, Mycobacterium bovis, Mycobacterium leprae, Mycobacterium tuberculosis, Mycoplasma genitalium, Mycoplasma pneumoniae, Neisseria gonorrhoeae, Neisseria meningitidis, Pasteurella*

multocida, Proteus mirabilis, Pseudomonas putida, Pseudomonas syringae, Salmonella paratyphi, Salmonella typhi, Staphylococcus epidermidis, Staphylococcus haemolyticus, Streptococcus mutans, Streptococcus pneumoniae, Streptococcus pyogenes, Treponema pallidum, Ureaplasma urealyticum, Vibrio cholerae or *Yersinia pestis* (including the nucleic acids of SEQ ID NOs.: 6214-

5   42397, the sequences complementary to the nucleic acids of SEQ ID NOs.: 6214-42397, and the polypeptides of SEQ ID NOs.: 42398-78581) can be used to identify homologous coding nucleic acids or homologous polypeptides required for proliferation from these and other organisms using methods such as nucleic acid hybridization and computer database analysis. Likewise, the antisense nucleic acids which inhibit proliferation of *Escherichia coli, Staphylococcus aureus,*

10   *Enterococcus faecalis, Klebsiella pneumoniae, Pseudomonas aeruginosa, Salmonella typhimurium, Acinetobacter baumannii, Bacillus anthracis, Bacteroides fragilis, Bordetella pertussis, Borrelia burgdorferi, Burkholderia cepacia, Burkholderia fungorum, Burkholderia mallei, Campylobacter jejuni, Chlamydia pneumoniae, Chlamydia trachomatis, Clostridium acetobutylicum, Clostridium botulinum, Clostridium difficile, Corynebacterium diptheriae, Enterobacter cloacae, Enterococcus*

15   *faecium, Haemophilus influenzae, Helicobacter pylori, Legionella pneumophila, Listeria monocytogenes, Moraxella catarrhalis, Mycobacterium avium, Mycobacterium bovis, Mycobacterium leprae, Mycobacterium tuberculosis, Mycoplasma genitalium, Mycoplasma pneumoniae, Neisseria gonorrhoeae, Neisseria meningitidis, Pasteurella multocida, Proteus mirabilis, Pseudomonas putida, Pseudomonas syringae, Salmonella paratyphi, Salmonella typhi,*

20   *Staphylococcus epidermidis, Staphylococcus haemolyticus, Streptococcus mutans, Streptococcus pneumoniae, Streptococcus pyogenes, Treponema pallidum, Ureaplasma urealyticum, Vibrio cholerae* or *Yersinia pestis* (including the antisense nucleic acids of SEQ ID NOs.: 1-6213 or the sequences complementary thereto) may also be used to identify antisense nucleic acids which inhibit proliferation of these and other microorganisms or cells using nucleic acid hybridization or

25   computer database analysis.

In one embodiment of the present invention, the nucleic acid sequences from *Escherichia coli, Staphylococcus aureus, Enterococcus faecalis, Klebsiella pneumoniae, Pseudomonas aeruginosa, Salmonella typhimurium, Acinetobacter baumannii, Bacillus anthracis, Bacteroides fragilis, Bordetella pertussis, Borrelia burgdorferi, Burkholderia cepacia, Burkholderia fungorum,*

30   *Burkholderia mallei, Campylobacter jejuni, Chlamydia pneumoniae, Chlamydia trachomatis, Clostridium acetobutylicum, Clostridium botulinum, Clostridium difficile, Corynebacterium diptheriae, Enterobacter cloacae, Enterococcus faecium, Haemophilus influenzae, Helicobacter pylori, Legionella pneumophila, Listeria monocytogenes, Moraxella catarrhalis, Mycobacterium avium, Mycobacterium bovis, Mycobacterium leprae, Mycobacterium tuberculosis, Mycoplasma*

35   *genitalium, Mycoplasma pneumoniae, Neisseria gonorrhoeae, Neisseria meningitidis, Pasteurella multocida, Proteus mirabilis, Pseudomonas putida, Pseudomonas syringae, Salmonella paratyphi, Salmonella typhi, Staphylococcus epidermidis, Staphylococcus haemolyticus, Streptococcus mutans, Streptococcus pneumoniae, Streptococcus pyogenes, Treponema pallidum, Ureaplasma*

urealyticum, Vibrio cholerae or *Yersinia pestis* (including the nucleic acids of SEQ ID NOs.: 6214-42397 and the antisense nucleic acids of SEQ ID NOs. 1-6213) are used to screen genomic libraries generated from *Escherichia coli, Staphylococcus aureus, Enterococcus faecalis, Klebsiella pneumoniae, Pseudomonas aeruginosa, Salmonella typhimurium, Acinetobacter baumannii,*

5   *Bacillus anthracis, Bacteroides fragilis, Bordetella pertussis, Borrelia burgdorferi, Burkholderia cepacia, Burkholderia fungorum, Burkholderia mallei, Campylobacter jejuni, Chlamydia pneumoniae, Chlamydia trachomatis, Clostridium acetobutylicum, Clostridium botulinum, Clostridium difficile, Corynebacterium diptheriae, Enterobacter cloacae, Enterococcus faecium, Haemophilus influenzae, Helicobacter pylori, Legionella pneumophila, Listeria monocytogenes,*

10   *Moraxella catarrhalis, Mycobacterium avium, Mycobacterium bovis, Mycobacterium leprae, Mycobacterium tuberculosis, Mycoplasma genitalium, Mycoplasma pneumoniae, Neisseria gonorrhoeae, Neisseria meningitidis, Pasteurella multocida, Proteus mirabilis, Pseudomonas putida, Pseudomonas syringae, Salmonella paratyphi, Salmonella typhi, Staphylococcus epidermidis, Staphylococcus haemolyticus, Streptococcus mutans, Streptococcus pneumoniae,*

15   *Streptococcus pyogenes, Treponema pallidum, Ureaplasma urealyticum, Vibrio cholerae, Yersinia pestis* and other bacterial species of interest. For example, the genomic library may be from Gram positive bacteria, Gram negative bacteria or other organisms including *Acinetobacter baumannii, Anaplasma marginale, Aspergillus fumigatus, Bacillus anthracis, Bacteroides fragilis, Bordetella pertussis, Borrelia burgdorferi, Burkholderia cepacia, Burkholderia fungorum, Burkholderia*

20   *mallei, Campylobacter jejuni, Candida albicans, Candida glabrata* (also called *Torulopsis glabrata*), *Candida tropicalis, Candida parapsilosis, Candida guilliermondii, Candida krusei, Candida kefyr* (also called *Candida pseudotropicalis*), *Candida dubliniensis, Chlamydia pneumoniae, Chlamydia trachomatis, Clostridium acetobutylicum, Clostridium botulinum, Clostridium difficile, Clostridium perfringens, Coccidioides immitis, Corynebacterium diptheriae,*

25   *Cryptococcus neoformans, Enterobacter cloacae, Enterococcus faecalis, Enterococcus faecium, Escherichia coli, Haemophilus influenzae, Helicobacter pylori, Histoplasma capsulatum, Klebsiella pneumoniae, Legionella pneumophila, Listeria monocytogenes, Moraxella catarrhalis, Mycobacterium avium, Mycobacterium bovis, Mycobacterium leprae, Mycobacterium tuberculosis, Mycoplasma genitalium, Mycoplasma pneumoniae, Neisseria gonorrhoeae, Neisseria meningitidis,*

30   *Nocardia asteroides, Pasteurella haemolytica, Pasteurella multocida, Pneumocystis carinii, Proteus mirabilis, Proteus vulgaris, Pseudomonas aeruginosa, Pseudomonas putida, Pseudomonas syringae, Salmonella bongori, Salmonella cholerasuis, Salmonella enterica, Salmonella paratyphi, Salmonella typhi, Salmonella typhimurium, Shigella boydii, Shigella dysenteriae, Shigella flexneri, Shigella sonnei, Staphylococcus aureus, Staphylococcus epidermidis, Staphylococcus haemolyticus,*

35   *Streptococcus pneumoniae, Streptococcus mutans, Streptococcus pyogenes, Treponema pallidum, Ureaplasma urealyticum, Vibrio cholerae, Vibrio parahaemolyticus, Vibrio vulnificans, Yersinia enterocolitica, Yersinia pestis* or any species falling within the genera of any of the above species, including coagulase negative species of *Staphylococcus.* In some embodiments, the genomic

library may be from an organism other than *E. coli*. Standard molecular biology techniques are used to generate genomic libraries from various cells or microorganisms. In one aspect, the libraries are generated and bound to nitrocellulose paper. The identified exogenous nucleic acid sequences of the present invention can then be used as probes to screen the libraries for homologous sequences.

5   For example, the libraries may be screened to identify homologous coding nucleic acids or homologous antisense nucleic acids comprising nucleotide sequences which hybridize under stringent conditions to a nucleic acid selected from the group consisting of SEQ ID NOs.: 1-6213, nucleic acids comprising nucleotide sequences which hybridize under stringent conditions to a fragment comprising at least 10, 15, 20, 25, 30, 35, 40, 50, 75, 100, 150, 200, 300, 400, or 500

10   consecutive nucleotides of one of SEQ ID NOs. 1-6213, nucleic acids comprising nucleotide sequences which hybridize under stringent conditions to a nucleic acid complementary to one of SEQ ID NOs. 1-6213, nucleic acids comprising nucleotide sequences which hybridize under stringent conditions to a fragment comprising at least 10, 15, 20, 25, 30, 35, 40, 50, 75, 100, 150, 200, 300, 400, or 500 consecutive nucleotides of the sequence complementary to one of SEQ ID NOs. 1-

15   6213, nucleic acids comprising nucleotide sequences which hybridize under stringent conditions to a nucleic acid selected from the group consisting of SEQ ID NOS.: 6214-42397, nucleic acids comprising nucleotide sequences which hybridize under stringent conditions to a fragment comprising at least 10, 15, 20, 25, 30, 35, 40, 50, 75, 100, 150, 200, 300, 400, or 500 consecutive nucleotides of one of SEQ ID NOS.: 6214-42397, nucleic acids comprising nucleotide sequences

20   which hybridize under stringent conditions to a nucleic acid complementary to one of SEQ ID NOS.: 6214-42397, nucleic acids comprising nucleotide sequences which hybridize under stringent conditions to a fragment comprising at least 10, 15, 20, 25, 30, 35, 40, 50, 75, 100, 150, 200, 300, 400, or 500 consecutive nucleotides of the sequence complementary to one of SEQ ID NOS.: 6214-42397.

25   The libraries may also be screened to identify homologous nucleic coding nucleic acids or homologous antisense nucleic acids comprising nucleotide sequences which hybridize under moderate conditions to a nucleic acid selected from the group consisting of SEQ ID NOs.: 1-6213, nucleic acids comprising nucleotide sequences which hybridize under moderate conditions to a fragment comprising at least 10, 15, 20, 25, 30, 35, 40, 50, 75, 100, 150, 200, 300, 400, or 500

30   consecutive nucleotides of one of SEQ ID NOs. 1-6213, nucleic acids comprising nucleotide sequences which hybridize under moderate conditions to a nucleic acid complementary to one of SEQ ID NOs. 1-6213, nucleic acids comprising nucleotide sequences which hybridize under moderate conditions to a fragment comprising at least 10, 15, 20, 25, 30, 35, 40, 50, 75, 100, 150, 200, 300, 400, or 500 consecutive nucleotides of the sequence complementary to one of SEQ ID

35   NOs. 1-6213, nucleic acids comprising nucleotide sequences which hybridize under moderate conditions to a nucleic acid selected from the group consisting of SEQ ID NOS.: 6214-42397, nucleic acids comprising nucleic acid sequences which hybridize under moderate conditions to a fragment comprising at least 10, 15, 20, 25, 30, 35, 40, 50, 75, 100, 150, 200, 300, 400, or 500

consecutive nucleotides of one of SEQ ID NOS.: 6214-42397, nucleic acids comprising nucleotide sequences which hybridize under moderate conditions to a nucleic acid complementary to one of SEQ ID NOS.: 6214-42397 and nucleic acids comprising nucleotide sequences which hybridize under moderate conditions to a fragment comprising at least 10, 15, 20, 25, 30, 35, 40, 50, 75, 100,

5   150, 200, 300, 400, or 500 consecutive nucleotides of the sequence complementary to one of SEQ ID NOS.: 6214-42397.

The homologous coding nucleic acids, homologous antisense nucleic acids or homologous polypeptides identified as above can then be used as targets or tools for the identification of new, antimicrobial compounds using methods such as those described herein. In some embodiments, the

10   homologous coding nucleic acids, homologous antisense nucleic acids, or homologous polypeptides may be used to identify compounds with activity against more than one microorganism. [Placeholder]

For example, the preceding methods may be used to isolate homologous coding nucleic acids or homologous antisense nucleic acids comprising a nucleotide sequence with at least 97%, at least 95%, at least 90%, at least 85%, at least 80%, or at least 70% nucleotide sequence identity to a

15   nucleotide sequence selected from the group consisting of one of the sequences of SEQ ID NOS. 1-6213, fragments comprising at least 10, 15, 20, 25, 30, 35, 40, 50, 75, 100, 150, 200, 300, 400, or 500 consecutive nucleotides thereof, and the sequences complementary thereto. The preceding methods may also be used to isolate homologous coding nucleic acids or homologous antisense nucleic acids comprising a nucleotide sequence with at least 97%, at least 95%, at least 90%, at least 85%, at

20   least 80%, or at least 70% nucleotide sequence identity to a nucleotide sequence selected from the group consisting of one of the nucleotide sequences of SEQ ID NOS.: 6214-42397, fragments comprising at least 10, 15, 20, 25, 30, 35, 40, 50, 75, 100, 150, 200, 300, 400, or 500 consecutive nucleotides thereof, and the sequences complementary thereto. Identity may be measured using BLASTN version 2.0 with the default parameters. (Altschul, S.F. et al. Gapped BLAST and PSI-

25   BLAST: A New Generation of Protein Database Search Programs, Nucleic Acid Res. 25: 3389-3402 (1997). For example, the homologous polynucleotides may comprise a coding sequence which is a naturally occurring allelic variant of one of the coding sequences described herein. Such allelic variants may have a substitution, deletion or addition of one or more nucleotides when compared to the nucleic acids of SEQ ID NOs: 1-6213, SEQ ID NOS.: 6214-42397 or the

30   nucleotide sequences complementary thereto.

Additionally, the above procedures may be used to isolate homologous coding nucleic acids which encode polypeptides having at least 99%, 95%, at least 90%, at least 85%, at least 80%, at least 70%, at least 60%, at least 50%, at least 40% or at least 25% amino acid identity or similarity to a polypeptide comprising the sequence of one of SEQ ID NOs: 42398-78581 or to a polypeptpide

35   whose expression is inhibited by a nucleic acid of one of SEQ ID NOs: 1-6213 or fragments comprising at least 5, 10, 15, 20, 25, 30, 35, 40, 50, 75, 100, or 150 consecutive amino acids thereof as determined using the FASTA version 3.0t78 algorithm with the default parameters. Alternatively, protein identity or similarity may be identified using BLASTP with the default

parameters, BLASTX with the default parameters, or TBLASTN with the default parameters. (Altschul, S.F. et al. Gapped BLAST and PSI-BLAST: A New Generation of Protein Database Search Programs, Nucleic Acid Res. 25: 3389-3402 (1997).

Alternatively, homologous coding nucleic acids, homologous antisense nucleic acids or homologous polypeptides may be identified by searching a database to identify sequences having a desired level of nucleotide or amino acid sequence homology to a nucleic acid or polypeptide involved in proliferation or an antisense nucleic acid to a nucleic acid involved in microbial proliferation. A variety of such databases are available to those skilled in the art, including GenBank and GenSeq. In some embodiments, the databases are screened to identify nucleic acids with at least 97%, at least 95%, at least 90%, at least 85%, at least 80%, or at least 70% nucleotide sequence identity to a nucleic acid required for proliferation, an antisense nucleic acid which inhibits proliferation, or a portion of a nucleic acid required for proliferation or a portion of an antisense nucleic acid which inhibits proliferation. For example, homologous coding sequences may be identified by using a database to identify nucleic acids homologous to one of SEQ ID Nos. 1-6213, homologous to fragments comprising at least 10, 15, 20, 25, 30, 35, 40, 50, 75, 100, 150, 200, 300, 400, or 500 consecutive nucleotides thereof, nucleic acids homologous to one of SEQ ID NOS.: 6214-42397, homologous to fragments comprising at least 10, 15, 20, 25, 30, 35, 40, 50, 75, 100, 150, 200, 300, 400, or 500 consecutive nucleotides of one of SEQ ID NOS.: 6214-42397, nucleic acids homologous to one of SEQ ID Nos. 1-6213, homologous to fragments comprising at least 10, 15, 20, 25, 30, 35, 40, 50, 75, 100, 150, 200, 300, 400, or 500 consecutive nucleotides thereof or nucleic acids homologous to the sequences complementary to any of the preceding nucleic acids. In other embodiments, the databases are screened to identify polypeptides having at least 99%, 95%, at least 90%, at least 85%, at least 80%, at least 70%, at least 60%, at least 50%, at least 40% or at least 25% amino acid sequence identity or similarity to a polypeptide involved in proliferation or a portion thereof. For example, the database may be screened to identify polypeptides homologous to a polypeptide comprising one of SEQ ID NOs: 42398-78581, a polypeptide whose expression is inhibited by a nucleic acid of one of SEQ ID NOs: 1-6213 or homologous to fragments comprising at least 5, 10, 15, 20, 25, 30, 35, 40, 50, 75, 100, or 150 consecutive amino acids of any of the preceding polypeptides. In some embodiments, the database may be screened to identify homologous coding nucleic acids, homologous antisense nucleic acids or homologous polypeptides from cells or microorganisms other than the *Escherichia coli, Staphylococcus aureus, Enterococcus faecalis, Klebsiella pneumoniae, Pseudomonas aeruginosa, Salmonella typhimurium, Acinetobacter baumannii, Bacillus anthracis, Bacteroides fragilis, Bordetella pertussis, Borrelia burgdorferi, Burkholderia cepacia, Burkholderia fungorum, Burkholderia mallei, Campylobacter jejuni, Chlamydia pneumoniae, Chlamydia trachomatis, Clostridium acetobutylicum, Clostridium botulinum, Clostridium difficile, Corynebacterium diptheriae, Enterobacter cloacae, Enterococcus faecium, Haemophilus influenzae, Helicobacter pylori, Legionella pneumophila, Listeria monocytogenes, Moraxella catarrhalis, Mycobacterium avium, Mycobacterium bovis,*

Mycobacterium leprae, Mycobacterium tuberculosis, Mycoplasma genitalium, Mycoplasma pneumoniae, Neisseria gonorrhoeae, Neisseria meningitidis, Pasteurella multocida, Proteus mirabilis, Pseudomonas putida, Pseudomonas syringae, Salmonella paratyphi, Salmonella typhi, Staphylococcus epidermidis, Staphylococcus haemolyticus, Streptococcus mutans, Streptococcus

5   *pneumoniae, Streptococcus pyogenes, Treponema pallidum, Ureaplasma urealyticum, Vibrio cholerae* or *Yersinia pestis* species from which they were obtained. For example the database may be screened to identify homologous coding nucleic acids, homologous antisense nucleic acids or homologous polypeptides from microorganisms such as *Acinetobacter baumannii, Anaplasma marginale, Aspergillus fumigatus, Bacillus anthracis, Bacteroides fragilis, Bordetella pertussis,*

10   *Borrelia burgdorferi, Burkholderia cepacia, Burkholderia fungorum, Burkholderia mallei, Campylobacter jejuni, Candida albicans, Candida glabrata* (also called *Torulopsis glabrata*), *Candida tropicalis, Candida parapsilosis, Candida guilliermondii, Candida krusei, Candida kefyr* (also called *Candida pseudotropicalis*), *Candida dubliniensis, Chlamydia pneumoniae, Chlamydia trachomatis, Clostridium acetobutylicum, Clostridium botulinum, Clostridium difficile, Clostridium*

15   *perfringens, Coccidioides immitis, Corynebacterium diptheriae, Cryptococcus neoformans, Enterobacter cloacae, Enterococcus faecalis, Enterococcus faecium, Escherichia coli, Haemophilus influenzae, Helicobacter pylori, Histoplasma capsulatum, Klebsiella pneumoniae, Legionella pneumophila, Listeria monocytogenes, Moraxella catarrhalis, Mycobacterium avium, Mycobacterium bovis, Mycobacterium leprae, Mycobacterium tuberculosis, Mycoplasma*

20   *genitalium, Mycoplasma pneumoniae, Neisseria gonorrhoeae, Neisseria meningitidis, Nocardia asteroides, Pasteurella haemolytica, Pasteurella multocida, Pneumocystis carinii, Proteus mirabilis, Proteus vulgaris, Pseudomonas aeruginosa, Pseudomonas putida, Pseudomonas syringae, Salmonella bongori, Salmonella cholerasuis, Salmonella enterica, Salmonella paratyphi, Salmonella typhi, Salmonella typhimurium, Shigella boydii, Shigella dysenteriae, Shigella flexneri,*

25   *Shigella sonnei, Staphylococcus aureus, Staphylococcus epidermidis, Staphylococcus haemolyticus, Streptococcus pneumoniae, Streptococcus mutans, Streptococcus pyogenes, Treponema pallidum, Ureaplasma urealyticum, Vibrio cholerae, Vibrio parahaemolyticus, Vibrio vulnificans, Yersinia enterocolitica, Yersinia pestis* or any species falling within the genera of any of the above species, including coagulase negative *Staphylococcus* . In some embodiments, the homologous coding

30   nucleic acids, homologous antisense nucleic acids, or homologous polypeptides are from an organism other than *E. coli.*

In another embodiment, gene expression arrays and microarrays can be employed. Gene expression arrays are high density arrays of DNA samples deposited at specific locations on a glass chip, nylon membrane, or the like. Such arrays can be used by researchers to quantify relative gene

35   expression under different conditions. Gene expression arrays are used by researchers to help identify optimal drug targets, profile new compounds, and determine disease pathways. An example of this technology is found in U.S. Patent No. 5,807,522.

It is possible to study the expression of all genes in the genome of a particular microbial organism using a single array. For example, the arrays may consist of 12 x 24 cm nylon filters containing PCR products corresponding to ORFs from *Escherichia coli*, *Staphylococcus aureus*, *Enterococcus faecalis*, *Klebsiella pneumoniae*, *Pseudomonas aeruginosa*, *Salmonella typhimurium*,

5   *Acinetobacter baumannii*, *Bacillus anthracis*, *Bacteroides fragilis*, *Bordetella pertussis*, *Borrelia burgdorferi*, *Burkholderia cepacia*, *Burkholderia fungorum*, *Burkholderia mallei*, *Campylobacter jejuni*, *Chlamydia pneumoniae*, *Chlamydia trachomatis*, *Clostridium acetobutylicum*, *Clostridium botulinum*, *Clostridium difficile*, *Corynebacterium diptheriae*, *Enterobacter cloacae*, *Enterococcus faecium*, *Haemophilus influenzae*, *Helicobacter pylori*, *Legionella pneumophila*, *Listeria*

10   *monocytogenes*, *Moraxella catarrhalis*, *Mycobacterium avium*, *Mycobacterium bovis*, *Mycobacterium leprae*, *Mycobacterium tuberculosis*, *Mycoplasma genitalium*, *Mycoplasma pneumoniae*, *Neisseria gonorrhoeae*, *Neisseria meningitidis*, *Pasteurella multocida*, *Proteus mirabilis*, *Pseudomonas putida*, *Pseudomonas syringae*, *Salmonella paratyphi*, *Salmonella typhi*, *Staphylococcus epidermidis*, *Staphylococcus haemolyticus*, *Streptococcus mutans*, *Streptococcus*

15   *pneumoniae*, *Streptococcus pyogenes*, *Treponema pallidum*, *Ureaplasma urealyticum*, *Vibrio cholerae* or *Yersinia pestis* (including the nucleic acids of SEQ ID NOs.: 6214-42397) . 10 ngs of each PCR product are spotted every 1.5 mm on the filter. Single stranded labeled cDNAs are prepared for hybridization to the array (no second strand synthesis or amplification step is done) and placed in contact with the filter. Thus the labeled cDNAs are of "antisense" orientation.

20   Quantitative analysis is done by phosphorimager.

Hybridization of cDNA made from a sample of total cell mRNA to such an array followed by detection of binding by one or more of various techniques known to those in the art results in a signal at each location on the array to which cDNA hybridized. The intensity of the hybridization signal obtained at each location in the array thus reflects the amount of mRNA for that specific

25   gene that was present in the sample. Comparing the results obtained for mRNA isolated from cells grown under different conditions thus allows for a comparison of the relative amount of expression of each individual gene during growth under the different conditions.

Gene expression arrays may be used to analyze the total mRNA expression pattern at various time points after induction of an antisense nucleic acid complementary to a proliferation-

30   required gene. Analysis of the expression pattern indicated by hybridization to the array provides information on other genes whose expression is influenced by antisense expression. For example, if the antisense is complementary to a gene for ribosomal protein L7/L12 in the 50S subunit, levels of other mRNAs may be observed to increase, decrease or stay the same following expression of antisense to the L7/L12 gene. If the antisense is complementary to a different 50S subunit

35   ribosomal protein mRNA (e.g. L25), a different mRNA expression pattern may result. Thus, the mRNA expression pattern observed following expression of an antisense nucleic acid comprising a nucleotide sequence complementary to a proliferation required gene may identify other proliferation-required nucleic acids. In addition, the mRNA expression patterns observed when the

bacteria are exposed to candidate drug compounds or known antibiotics may be compared to those observed with antisense nucleic acids comprising a nucleotide sequence complementary to a proliferation-required nucleic acid. If the mRNA expression pattern observed with the candidate drug compound is similar to that observed with the antisense nucleic acid, the drug compound may

5   be a promising therapeutic candidate. Thus, the assay would be useful in assisting in the selection of promising candidate drug compounds for use in drug development.

In cases where the source of nucleic acid deposited on the array and the source of the nucleic acid being hybridized to the array are from two different cells or microorganisms, gene expression arrays can identify homologous nucleic acids in the two cells or microorganisms.

10   The present invention also contemplates additional methods for screening other microorganisms for proliferation-required genes. In one aspect of this embodiment, an antisense nucleic acid comprising a nucleotide sequence complementary to the proliferation-required sequences from *Escherichia coli, Staphylococcus aureus, Enterococcus faecalis, Klebsiella pneumoniae, Pseudomonas aeruginosa, Salmonella typhimurium, Acinetobacter baumannii, Bacillus anthracis,*

15   *Bacteroides fragilis, Bordetella pertussis, Borrelia burgdorferi, Burkholderia cepacia, Burkholderia fungorum, Burkholderia mallei, Campylobacter jejuni, Chlamydia pneumoniae, Chlamydia trachomatis, Clostridium acetobutylicum, Clostridium botulinum, Clostridium difficile, Corynebacterium diptheriae, Enterobacter cloacae, Enterococcus faecium, Haemophilus influenzae, Helicobacter pylori, Legionella pneumophila, Listeria monocytogenes, Moraxella*

20   *catarrhalis, Mycobacterium avium, Mycobacterium bovis, Mycobacterium leprae, Mycobacterium tuberculosis, Mycoplasma genitalium, Mycoplasma pneumoniae, Neisseria gonorrhoeae, Neisseria meningitidis, Pasteurella multocida, Proteus mirabilis, Pseudomonas putida, Pseudomonas syringae, Salmonella paratyphi, Salmonella typhi, Staphylococcus epidermidis, Staphylococcus haemolyticus, Streptococcus mutans, Streptococcus pneumoniae, Streptococcus pyogenes,*

25   *Treponema pallidum, Ureaplasma urealyticum, Vibrio cholerae* or *Yersinia pestis,* or a portion thereof, is transcribed in an antisense orientation in such a way as to alter the level or activity of a nucleic acid required for proliferation of an autologous or heterologous cell or microorganism. For example, the antisense nucleic acid may be a homologous antisense nucleic acid such as an antisense nucleic acid homologous to the nucleotide sequence complementary to one of SEQ ID NOs.: 6214-

30   42397, an antisense nucleic acid comprising a nucleotide sequence homologous to one of SEQ ID Nos.: 1-6213, or an antisense nucleic acid comprising a nucleotide sequence complementary to a portion of any of the preceding nucleic acids. The cell or microorganism transcribing the homologous antisense nucleic acid may be used in a cell-based assay, such as those described herein, to identify candidate antibiotic compounds. In another embodiment, the conserved portions of nucleotide

35   sequences identified as proliferation-required can be used to generate degenerate primers for use in the polymerase chain reaction (PCR). The PCR technique is well known in the art. The successful production of a PCR product using degenerate primers generated from the nucleotide sequences identified herein indicates the presence of a homologous gene sequence in the species being screened.

This homologous gene is then isolated, expressed, and used as a target for candidate antibiotic compounds. In another aspect of this embodiment, the homologous gene (for example a homologous coding nucleic acid) thus identified, or a portion thereof, is transcribed in an autologous cell or microorganism or in a heterologous cell or microorganism in an antisense orientation in such a way as to alter the level or activity of a homologous gene required for proliferation in the autologous or heterologous cell or microorganism. Alternatively, a homologous antisense nucleic acid may be transcribed in an autologous or heterologous cell or microorganism in such a way as to alter the level or activity of a gene product required for proliferation in the autologous or heterologous cell or microorganism.

The nucleic acids homologous to the genes required for the proliferation of *Escherichia coli, Staphylococcus aureus, Enterococcus faecalis, Klebsiella pneumoniae, Pseudomonas aeruginosa, Salmonella typhimurium, Acinetobacter baumannii, Bacillus anthracis, Bacteroides fragilis, Bordetella pertussis, Borrelia burgdorferi, Burkholderia cepacia, Burkholderia fungorum, Burkholderia mallei, Campylobacter jejuni, Chlamydia pneumoniae, Chlamydia trachomatis, Clostridium acetobutylicum, Clostridium botulinum, Clostridium difficile, Corynebacterium diptheriae, Enterobacter cloacae, Enterococcus faecium, Haemophilus influenzae, Helicobacter pylori, Legionella pneumophila, Listeria monocytogenes, Moraxella catarrhalis, Mycobacterium avium, Mycobacterium bovis, Mycobacterium leprae, Mycobacterium tuberculosis, Mycoplasma genitalium, Mycoplasma pneumoniae, Neisseria gonorrhoeae, Neisseria meningitidis, Pasteurella multocida, Proteus mirabilis, Pseudomonas putida, Pseudomonas syringae, Salmonella paratyphi, Salmonella typhi, Staphylococcus epidermidis, Staphylococcus haemolyticus, Streptococcus mutans, Streptococcus pneumoniae, Streptococcus pyogenes, Treponema pallidum, Ureaplasma urealyticum, Vibrio cholerae* or *Yersinia pestis* or the sequences complementary thereto may be used to identify homologous coding nucleic acids or homologous antisense nucleic acids from cells or microorganisms other than *Escherichia coli, Staphylococcus aureus, Enterococcus faecalis, Klebsiella pneumoniae, Pseudomonas aeruginosa, Salmonella typhimurium, Acinetobacter baumannii, Bacillus anthracis, Bacteroides fragilis, Bordetella pertussis, Borrelia burgdorferi, Burkholderia cepacia, Burkholderia fungorum, Burkholderia mallei, Campylobacter jejuni, Chlamydia pneumoniae, Chlamydia trachomatis, Clostridium acetobutylicum, Clostridium botulinum, Clostridium difficile, Corynebacterium diptheriae, Enterobacter cloacae, Enterococcus faecium, Haemophilus influenzae, Helicobacter pylori, Legionella pneumophila, Listeria monocytogenes, Moraxella catarrhalis, Mycobacterium avium, Mycobacterium bovis, Mycobacterium leprae, Mycobacterium tuberculosis, Mycoplasma genitalium, Mycoplasma pneumoniae, Neisseria gonorrhoeae, Neisseria meningitidis, Pasteurella multocida, Proteus mirabilis, Pseudomonas putida, Pseudomonas syringae, Salmonella paratyphi, Salmonella typhi, Staphylococcus epidermidis, Staphylococcus haemolyticus, Streptococcus mutans, Streptococcus pneumoniae, Streptococcus pyogenes, Treponema pallidum, Ureaplasma urealyticum, Vibrio cholerae* or *Yersinia pestis* to inhibit the proliferation of cells or microorganisms other than

Escherichia coli, Staphylococcus aureus, Enterococcus faecalis, Klebsiella pneumoniae, Pseudomonas aeruginosa, Salmonella typhimurium, Acinetobacter baumannii, Bacillus anthracis, Bacteroides fragilis, Bordetella pertussis, Borrelia burgdorferi, Burkholderia cepacia, Burkholderia fungorum, Burkholderia mallei, Campylobacter jejuni, Chlamydia pneumoniae,

5   *Chlamydia trachomatis, Clostridium acetobutylicum, Clostridium botulinum, Clostridium difficile, Corynebacterium diptheriae, Enterobacter cloacae, Enterococcus faecium, Haemophilus influenzae, Helicobacter pylori, Legionella pneumophila, Listeria monocytogenes, Moraxella catarrhalis, Mycobacterium avium, Mycobacterium bovis, Mycobacterium leprae, Mycobacterium tuberculosis, Mycoplasma genitalium, Mycoplasma pneumoniae, Neisseria gonorrhoeae, Neisseria*

10   *meningitidis, Pasteurella multocida, Proteus mirabilis, Pseudomonas putida, Pseudomonas syringae, Salmonella paratyphi, Salmonella typhi, Staphylococcus epidermidis, Staphylococcus haemolyticus, Streptococcus mutans, Streptococcus pneumoniae, Streptococcus pyogenes, Treponema pallidum, Ureaplasma urealyticum, Vibrio cholerae* or *Yersinia pestis* by inhibiting the activity or reducing the amount of the identified homologous coding nucleic acid or homologous

15   polypeptide in the cell or microorganism other than *Escherichia coli, Staphylococcus aureus, Enterococcus faecalis, Klebsiella pneumoniae, Pseudomonas aeruginosa, Salmonella typhimurium, Acinetobacter baumannii, Bacillus anthracis, Bacteroides fragilis, Bordetella pertussis, Borrelia burgdorferi, Burkholderia cepacia, Burkholderia fungorum, Burkholderia mallei, Campylobacter jejuni, Chlamydia pneumoniae, Chlamydia trachomatis, Clostridium acetobutylicum, Clostridium*

20   *botulinum, Clostridium difficile, Corynebacterium diptheriae, Enterobacter cloacae, Enterococcus faecium, Haemophilus influenzae, Helicobacter pylori, Legionella pneumophila, Listeria monocytogenes, Moraxella catarrhalis, Mycobacterium avium, Mycobacterium bovis, Mycobacterium leprae, Mycobacterium tuberculosis, Mycoplasma genitalium, Mycoplasma pneumoniae, Neisseria gonorrhoeae, Neisseria meningitidis, Pasteurella multocida, Proteus*

25   *mirabilis, Pseudomonas putida, Pseudomonas syringae, Salmonella paratyphi, Salmonella typhi, Staphylococcus epidermidis, Staphylococcus haemolyticus, Streptococcus mutans, Streptococcus pneumoniae, Streptococcus pyogenes, Treponema pallidum, Ureaplasma urealyticum, Vibrio cholerae* or *Yersinia pestis* or to identify compounds which inhibit the growth of cells or microorganisms other than *Escherichia coli, Staphylococcus aureus, Enterococcus faecalis,*

30   *Klebsiella pneumoniae, Pseudomonas aeruginosa, Salmonella typhimurium, Acinetobacter baumannii, Bacillus anthracis, Bacteroides fragilis, Bordetella pertussis, Borrelia burgdorferi, Burkholderia cepacia, Burkholderia fungorum, Burkholderia mallei, Campylobacter jejuni, Chlamydia pneumoniae, Chlamydia trachomatis, Clostridium acetobutylicum, Clostridium botulinum, Clostridium difficile, Corynebacterium diptheriae, Enterobacter cloacae, Enterococcus*

35   *faecium, Haemophilus influenzae, Helicobacter pylori, Legionella pneumophila, Listeria monocytogenes, Moraxella catarrhalis, Mycobacterium avium, Mycobacterium bovis, Mycobacterium leprae, Mycobacterium tuberculosis, Mycoplasma genitalium, Mycoplasma pneumoniae, Neisseria gonorrhoeae, Neisseria meningitidis, Pasteurella multocida, Proteus*

mirabilis, Pseudomonas putida, Pseudomonas syringae, Salmonella paratyphi, Salmonella typhi, Staphylococcus epidermidis, Staphylococcus haemolyticus, Streptococcus mutans, Streptococcus pneumoniae, Streptococcus pyogenes, Treponema pallidum, Ureaplasma urealyticum, Vibrio cholerae or *Yersinia pestis* as described below. For example, the nucleic acids homologous to

5   proliferation-required genes from *Escherichia coli, Staphylococcus aureus, Enterococcus faecalis, Klebsiella pneumoniae, Pseudomonas aeruginosa, Salmonella typhimurium, Acinetobacter baumannii, Bacillus anthracis, Bacteroides fragilis, Bordetella pertussis, Borrelia burgdorferi, Burkholderia cepacia, Burkholderia fungorum, Burkholderia mallei, Campylobacter jejuni, Chlamydia pneumoniae, Chlamydia trachomatis, Clostridium acetobutylicum, Clostridium*

10   *botulinum, Clostridium difficile, Corynebacterium diptheriae, Enterobacter cloacae, Enterococcus faecium, Haemophilus influenzae, Helicobacter pylori, Legionella pneumophila, Listeria monocytogenes, Moraxella catarrhalis, Mycobacterium avium, Mycobacterium bovis, Mycobacterium leprae, Mycobacterium tuberculosis, Mycoplasma genitalium, Mycoplasma pneumoniae, Neisseria gonorrhoeae, Neisseria meningitidis, Pasteurella multocida, Proteus*

15   *mirabilis, Pseudomonas putida, Pseudomonas syringae, Salmonella paratyphi, Salmonella typhi, Staphylococcus epidermidis, Staphylococcus haemolyticus, Streptococcus mutans, Streptococcus pneumoniae, Streptococcus pyogenes, Treponema pallidum, Ureaplasma urealyticum, Vibrio cholerae* or *Yersinia pestis* or the sequences complementary thereto may be used to identify compounds which inhibit the growth of *Acinetobacter baumannii, Anaplasma marginale,*

20   *Aspergillus fumigatus, Bacillus anthracis, Bacteroides fragilis, Bordetella pertussis, Borrelia burgdorferi, Burkholderia cepacia, Burkholderia fungorum, Burkholderia mallei, Campylobacter jejuni, Candida albicans, Candida glabrata* (also called *Torulopsis glabrata*), *Candida tropicalis, Candida parapsilosis, Candida guilliermondii, Candida krusei, Candida kefyr* (also called *Candida pseudotropicalis*), *Candida dubliniensis, Chlamydia pneumoniae, Chlamydia trachomatis,*

25   *Clostridium acetobutylicum, Clostridium botulinum, Clostridium difficile, Clostridium perfringens, Coccidioides immitis, Corynebacterium diptheriae, Cryptococcus neoformans, Enterobacter cloacae, Enterococcus faecalis, Enterococcus faecium, Escherichia coli, Haemophilus influenzae, Helicobacter pylori, Histoplasma capsulatum, Klebsiella pneumoniae, Legionella pneumophila, Listeria monocytogenes, Moraxella catarrhalis, Mycobacterium avium, Mycobacterium bovis,*

30   *Mycobacterium leprae, Mycobacterium tuberculosis, Mycoplasma genitalium, Mycoplasma pneumoniae, Neisseria gonorrhoeae, Neisseria meningitidis, Nocardia asteroides, Pasteurella haemolytica, Pasteurella multocida, Pneumocystis carinii, Proteus mirabilis, Proteus vulgaris, Pseudomonas aeruginosa, Pseudomonas putida, Pseudomonas syringae, Salmonella bongori, Salmonella cholerasuis, Salmonella enterica, Salmonella paratyphi, Salmonella typhi, Salmonella*

35   *typhimurium, Shigella boydii, Shigella dysenteriae, Shigella flexneri, Shigella sonnei, Staphylococcus aureus, Staphylococcus epidermidis, Staphylococcus haemolyticus, Streptococcus pneumoniae, Streptococcus mutans, Streptococcus pyogenes, Treponema pallidum, Ureaplasma urealyticum, Vibrio cholerae, Vibrio parahaemolyticus, Vibrio vulnificans, Yersinia enterocolitica,*

Yersinia pestis or any species falling within the genera of any of the above species. In some embodiments of the present invention, the nucleic acids homologous to proliferation-required sequences from *Escherichia coli, Staphylococcus aureus, Enterococcus faecalis, Klebsiella pneumoniae, Pseudomonas aeruginosa, Salmonella typhimurium, Acinetobacter baumannii,*

5   *Bacillus anthracis, Bacteroides fragilis, Bordetella pertussis, Borrelia burgdorferi, Burkholderia cepacia, Burkholderia fungorum, Burkholderia mallei, Campylobacter jejuni, Chlamydia pneumoniae, Chlamydia trachomatis, Clostridium acetobutylicum, Clostridium botulinum, Clostridium difficile, Corynebacterium diptheriae, Enterobacter cloacae, Enterococcus faecium, Haemophilus influenzae, Helicobacter pylori, Legionella pneumophila, Listeria monocytogenes,*

10   *Moraxella catarrhalis, Mycobacterium avium, Mycobacterium bovis, Mycobacterium leprae, Mycobacterium tuberculosis, Mycoplasma genitalium, Mycoplasma pneumoniae, Neisseria gonorrhoeae, Neisseria meningitidis, Pasteurella multocida, Proteus mirabilis, Pseudomonas putida, Pseudomonas syringae, Salmonella paratyphi, Salmonella typhi, Staphylococcus epidermidis, Staphylococcus haemolyticus, Streptococcus mutans, Streptococcus pneumoniae,*

15   *Streptococcus pyogenes, Treponema pallidum, Ureaplasma urealyticum, Vibrio cholerae* or *Yersinia pestis* (including nucleic acids homologous to one of SEQ ID NOs.: 6214-42397) or the sequences complementary thereto (including nucleic acids homologous to one of SEQ ID NOs.: 1-6213) are used to identify proliferation-required sequences in an organism other than *E. coli.*

In another embodiment of the present invention, antisense nucleic acids complementary to the

20   sequences identified as required for proliferation or portions thereof (including antisense nucleic acids comprising a nucleotide sequence complementary to one of SEQ ID NOs.: 6214-42397 or portions thereof, such as the nucleic acids of SEQ ID NOs.: 1-6213) are transferred to vectors capable of function within a species other than the species from which the sequences were obtained. For example, the vector may be functional in *Acinetobacter baumannii, Anaplasma marginale,*

25   *Aspergillus fumigatus, Bacillus anthracis, Bacteroides fragilis, Bordetella pertussis, Borrelia burgdorferi, Burkholderia cepacia, Burkholderia fungorum, Burkholderia mallei, Campylobacter jejuni, Candida albicans, Candida glabrata* (also called *Torulopsis glabrata*), *Candida tropicalis, Candida parapsilosis, Candida guilliermondii, Candida krusei, Candida kefyr* (also called *Candida pseudotropicalis*), *Candida dubliniensis, Chlamydia pneumoniae, Chlamydia trachomatis,*

30   *Clostridium acetobutylicum, Clostridium botulinum, Clostridium difficile, Clostridium perfringens, Coccidioides immitis, Corynebacterium diptheriae, Cryptococcus neoformans, Enterobacter cloacae, Enterococcus faecalis, Enterococcus faecium, Escherichia coli, Haemophilus influenzae, Helicobacter pylori, Histoplasma capsulatum, Klebsiella pneumoniae, Legionella pneumophila, Listeria monocytogenes, Moraxella catarrhalis, Mycobacterium avium, Mycobacterium bovis,*

35   *Mycobacterium leprae, Mycobacterium tuberculosis, Mycoplasma genitalium, Mycoplasma pneumoniae, Neisseria gonorrhoeae, Neisseria meningitidis, Nocardia asteroides, Pasteurella haemolytica, Pasteurella multocida, Pneumocystis carinii, Proteus mirabilis, Proteus vulgaris, Pseudomonas aeruginosa, Pseudomonas putida, Pseudomonas syringae, Salmonella bongori,*

Salmonella cholerasuis, Salmonella enterica, Salmonella paratyphi, Salmonella typhi, Salmonella typhimurium, Shigella boydii, Shigella dysenteriae, Shigella flexneri, Shigella sonnei, Staphylococcus aureus, Staphylococcus epidermidis, Staphylococcus haemolyticus, Streptococcus pneumoniae, Streptococcus mutans, Streptococcus pyogenes, Treponema pallidum, Ureaplasma

5   *urealyticum, Vibrio cholerae, Vibrio parahaemolyticus, Vibrio vulnificans, Yersinia enterocolitica, Yersinia pestis* or any species falling within the genera of any of the above species. In some embodiments of the present invention, the vector may be functional in an organism other than *E. coli*. As would be appreciated by one of ordinary skill in the art, vectors may contain certain elements that are species specific. These elements can include promoter sequences, operator

10   sequences, repressor genes, origins of replication, ribosomal binding sequences, termination sequences, and others. To use the antisense nucleic acids, one of ordinary skill in the art would know to use standard molecular biology techniques to isolate vectors containing the sequences of interest from cultured bacterial cells, isolate and purify those sequences, and subclone those sequences into a vector adapted for use in the species of bacteria to be screened.

15   Vectors for a variety of other species are known in the art. For example, numerous vectors which function in *E. coli* are known in the art. Also, Pla et al. have reported an expression vector that is functional in a number of relevant hosts including: *Salmonella typhimurium, Pseudomonas putida, and Pseudomonas aeruginosa. J. Bacteriol.* 172(8):4448-55 (1990). Brunschwig and Darzins (Gene (1992) 111:35-4, described a shuttle expression vector for *Pseudomonas aeruginosa.*

20   Vectors useful for the production of stabilized mRNA having an increased lifetime (including antisense RNA) in Gram negative organisms are described in U.S. Provisional Patent Application Serial Number 60/343,512, filed December 21, 2001. Similarly many examples exist of expression vectors that are freely transferable among various Gram positive microorganisms. Expression vectors for *Enterococcus faecalis* may be engineered by incorporating suitable promoters into a

25   pAK80 backbone (Israelsen, H., S. M. Madsen, A. Vrang, E. B. Hansen and E. Johansen. 1995. *Appl. Environ. Microbiol.* 61:2540-2547. A number of vectors useful for nucleic acid expression (including antisense nucleic acid expression) in *Enterococcus faecalis, Staphylococcus areus* as well as other Gram positive organisms are described in U.S. Patent Application Serial Number 10/032,393, filed December 21, 2001.

30   Following the subcloning of the antisense nucleic acids complementary to proliferation-required sequences from *Escherichia coli, Staphylococcus aureus, Enterococcus faecalis, Klebsiella pneumoniae, Pseudomonas aeruginosa, Salmonella typhimurium, Acinetobacter baumannii, Bacillus anthracis, Bacteroides fragilis, Bordetella pertussis, Borrelia burgdorferi, Burkholderia cepacia, Burkholderia fungorum, Burkholderia mallei, Campylobacter jejuni,*

35   *Chlamydia pneumoniae, Chlamydia trachomatis, Clostridium acetobutylicum, Clostridium botulinum, Clostridium difficile, Corynebacterium diptheriae, Enterobacter cloacae, Enterococcus faecium, Haemophilus influenzae, Helicobacter pylori, Legionella pneumophila, Listeria monocytogenes, Moraxella catarrhalis, Mycobacterium avium, Mycobacterium bovis,*

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Mycobacterium leprae, Mycobacterium tuberculosis, Mycoplasma genitalium, Mycoplasma pneumoniae, Neisseria gonorrhoeae, Neisseria meningitidis, Pasteurella multocida, Proteus mirabilis, Pseudomonas putida, Pseudomonas syringae, Salmonella paratyphi, Salmonella typhi, Staphylococcus epidermidis, Staphylococcus haemolyticus, Streptococcus mutans, Streptococcus

5   *pneumoniae, Streptococcus pyogenes, Treponema 'pallidum, Ureaplasma urealyticum, Vibrio cholerae* or *Yersinia pestis* or portions thereof into a vector functional in a second cell or microorganism of interest (i.e. a cell or microorganism other than the one from which the identified nucleic acids were obtained), the antisense nucleic acids are conditionally transcribed to test for bacterial growth inhibition. The nucleotide sequences of the nucleic acids from *Escherichia coli,*

10   *Staphylococcus aureus, Enterococcus faecalis, Klebsiella pneumoniae, Pseudomonas aeruginosa, Salmonella typhimurium, Acinetobacter baumannii, Bacillus anthracis, Bacteroides fragilis, Bordetella pertussis, Borrelia burgdorferi, Burkholderia cepacia, Burkholderia fungorum, Burkholderia mallei, Campylobacter jejuni, Chlamydia pneumoniae, Chlamydia trachomatis, Clostridium acetobutylicum, Clostridium botulinum, Clostridium difficile, Corynebacterium*

15   *diptheriae, Enterobacter cloacae, Enterococcus faecium, Haemophilus influenzae, Helicobacter pylori, Legionella pneumophila, Listeria monocytogenes, Moraxella catarrhalis, Mycobacterium avium, Mycobacterium bovis, Mycobacterium leprae, Mycobacterium tuberculosis, Mycoplasma genitalium, Mycoplasma pneumoniae, Neisseria gonorrhoeae, Neisseria meningitidis, Pasteurella multocida, Proteus mirabilis, Pseudomonas putida, Pseudomonas syringae, Salmonella paratyphi,*

20   *Salmonella typhi, Staphylococcus epidermidis, Staphylococcus haemolyticus, Streptococcus mutans, Streptococcus pneumoniae, Streptococcus pyogenes, Treponema pallidum, Ureaplasma urealyticum, Vibrio cholerae* or *Yersinia pestis* that, when transcribed, inhibit growth of the second cell or microorganism are compared to the known genomic sequence of the second cell or microorganism to identify the homologous gene from the second organism. If the homologous

25   sequence from the second cell or microorganism is not known, it may be identified and isolated by hybridization to the proliferation-required *Escherichia coli, Staphylococcus aureus, Enterococcus faecalis, Klebsiella pneumoniae, Pseudomonas aeruginosa, Salmonella typhimurium, Acinetobacter baumannii, Bacillus anthracis, Bacteroides fragilis, Bordetella pertussis, Borrelia burgdorferi, Burkholderia cepacia, Burkholderia fungorum, Burkholderia mallei, Campylobacter jejuni,*

30   *Chlamydia pneumoniae, Chlamydia trachomatis, Clostridium acetobutylicum, Clostridium botulinum, Clostridium difficile, Corynebacterium diptheriae, Enterobacter cloacae, Enterococcus faecium, Haemophilus influenzae, Helicobacter pylori, Legionella pneumophila, Listeria monocytogenes, Moraxella catarrhalis, Mycobacterium avium, Mycobacterium bovis, Mycobacterium leprae, Mycobacterium tuberculosis, Mycoplasma genitalium, Mycoplasma*

35   *pneumoniae, Neisseria gonorrhoeae, Neisseria meningitidis, Pasteurella multocida, Proteus mirabilis, Pseudomonas putida, Pseudomonas syringae, Salmonella paratyphi, Salmonella typhi, Staphylococcus epidermidis, Staphylococcus haemolyticus, Streptococcus mutans, Streptococcus pneumoniae, Streptococcus pyogenes, Treponema pallidum, Ureaplasma urealyticum, Vibrio*

cholerae or *Yersinia pestis* sequence of interest or by amplification using PCR primers based on the proliferation-required nucleotide sequence of interest as described above. In this way, sequences which may be required for the proliferation of the second cell or microorganism may be identified. For example, the second microorganism may be *Acinetobacter baumannii, Anaplasma marginale,*

5   *Aspergillus fumigatus, Bacillus anthracis, Bacteroides fragilis, Bordetella pertussis, Borrelia burgdorferi, Burkholderia cepacia, Burkholderia fungorum, Burkholderia mallei, Campylobacter jejuni, Candida albicans, Candida glabrata* (also called *Torulopsis glabrata*), *Candida tropicalis, Candida parapsilosis, Candida guilliermondii, Candida krusei, Candida kefyr* (also called *Candida pseudotropicalis*), *Candida dubliniensis, Chlamydia pneumoniae, Chlamydia trachomatis,*

10   *Clostridium acetobutylicum, Clostridium botulinum, Clostridium difficile, Clostridium perfringens, Coccidioides immitis, Corynebacterium diptheriae, Cryptococcus neoformans, Enterobacter cloacae, Enterococcus faecalis, Enterococcus faecium, Escherichia coli, Haemophilus influenzae, Helicobacter pylori, Histoplasma capsulatum, Klebsiella pneumoniae, Legionella pneumophila, Listeria monocytogenes, Moraxella catarrhalis, Mycobacterium avium, Mycobacterium bovis,*

15   *Mycobacterium leprae, Mycobacterium tuberculosis, Mycoplasma genitalium, Mycoplasma pneumoniae, Neisseria gonorrhoeae, Neisseria meningitidis, Nocardia asteroides, Pasteurella haemolytica, Pasteurella multocida, Pneumocystis carinii, Proteus mirabilis, Proteus vulgaris, Pseudomonas aeruginosa, Pseudomonas putida, Pseudomonas syringae, Salmonella bongori, Salmonella cholerasuis, Salmonella enterica, Salmonella paratyphi, Salmonella typhi, Salmonella*

20   *typhimurium, Shigella boydii, Shigella dysenteriae, Shigella flexneri, Shigella sonnei, Staphylococcus aureus, Staphylococcus epidermidis, Staphylococcus haemolyticus, Streptococcus pneumoniae, Streptococcus mutans, Streptococcus pyogenes, Treponema pallidum, Ureaplasma urealyticum, Vibrio cholerae, Vibrio parahaemolyticus, Vibrio vulnificans, Yersinia enterocolitica,* . *Yersinia pestis* or any species falling within the genera of any of the above species. In some

25   embodiments of the present invention, the second microorganism is an organism other than E. coli.

The homologous nucleic acid sequences from the second cell or microorganism which are identified as described above may then be operably linked to a promoter, such as an inducible promoter, in an antisense orientation and introduced into the second cell or microorganism. The techniques described herein for identifying *Escherichia coli, Staphylococcus aureus, Enterococcus*

30   *faecalis, Klebsiella pneumoniae, Pseudomonas aeruginosa, Salmonella typhimurium, Acinetobacter baumannii, Bacillus anthracis, Bacteroides fragilis, Bordetella pertussis, Borrelia burgdorferi, Burkholderia cepacia, Burkholderia fungorum, Burkholderia mallei, Campylobacter jejuni, Chlamydia pneumoniae, Chlamydia trachomatis, Clostridium acetobutylicum, Clostridium botulinum, Clostridium difficile, Corynebacterium diptheriae, Enterobacter cloacae, Enterococcus*

35   *faecium, Haemophilus influenzae, Helicobacter pylori, Legionella pneumophila, Listeria monocytogenes, Moraxella catarrhalis, Mycobacterium avium, Mycobacterium bovis, Mycobacterium leprae, Mycobacterium tuberculosis, Mycoplasma genitalium, Mycoplasma pneumoniae, Neisseria gonorrhoeae, Neisseria meningitidis, Pasteurella multocida, Proteus*

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mirabilis, Pseudomonas putida, Pseudomonas syringae, Salmonella paratyphi, Salmonella typhi, Staphylococcus epidermidis, Staphylococcus haemolyticus, Streptococcus mutans, Streptococcus pneumoniae, Streptococcus pyogenes, Treponema pallidum, Ureaplasma urealyticum, Vibrio cholerae or *Yersinia pestis* genes required for proliferation may thus be employed to determine

5   whether the identified nucleotide sequences from a second cell or microorganism inhibit the proliferation of the second cell or microorganism. For example, the second microorganism may be *Acinetobacter baumannii, Anaplasma marginale, Aspergillus fumigatus, Bacillus anthracis, Bacteroides fragilis, Bordetella pertussis, Borrelia burgdorferi, Burkholderia cepacia, Burkholderia fungorum, Burkholderia mallei, Campylobacter jejuni, Candida albicans, Candida*

10   *glabrata* (also called *Torulopsis glabrata*), *Candida tropicalis, Candida parapsilosis, Candida guilliermondii, Candida krusei, Candida kefyr* (also called *Candida pseudotropicalis*), *Candida dubliniensis, Chlamydia pneumoniae, Chlamydia trachomatis, Clostridium acetobutylicum, Clostridium botulinum, Clostridium difficile, Clostridium perfringens, Coccidioides immitis, Corynebacterium diptheriae, Cryptococcus neoformans, Enterobacter cloacae, Enterococcus*

15   *faecalis, Enterococcus faecium, Escherichia coli, Haemophilus influenzae, Helicobacter pylori, Histoplasma capsulatum, Klebsiella pneumoniae, Legionella pneumophila, Listeria monocytogenes, Moraxella catarrhalis, Mycobacterium avium, Mycobacterium bovis, Mycobacterium leprae, Mycobacterium tuberculosis, Mycoplasma genitalium, Mycoplasma pneumoniae, Neisseria gonorrhoeae, Neisseria meningitidis, Nocardia asteroides, Pasteurella*

20   *haemolytica, Pasteurella multocida, Pneumocystis carinii, Proteus mirabilis, Proteus vulgaris, Pseudomonas aeruginosa, Pseudomonas putida, Pseudomonas syringae, Salmonella bongori, Salmonella cholerasuis, Salmonella enterica, Salmonella paratyphi, Salmonella typhi, Salmonella typhimurium, Shigella boydii, Shigella dysenteriae, Shigella flexneri, Shigella sonnei, Staphylococcus aureus, Staphylococcus epidermidis, Staphylococcus haemolyticus, Streptococcus*

25   *pneumoniae, Streptococcus mutans, Streptococcus pyogenes, Treponema pallidum, Ureaplasma urealyticum, Vibrio cholerae, Vibrio parahaemolyticus, Vibrio vulnificans, Yersinia enterocolitica, Yersinia pestis* or any species falling within the genera of any of the above species. In some embodiments of the present invention, the second microorganism may be an organism other than E. coli.

30   Antisense nucleic acids required for the proliferation of microorganisms other than *Escherichia coli, Staphylococcus aureus, Enterococcus faecalis, Klebsiella pneumoniae, Pseudomonas aeruginosa, Salmonella typhimurium, Acinetobacter baumannii, Bacillus anthracis, Bacteroides fragilis, Bordetella pertussis, Borrelia burgdorferi, Burkholderia cepacia, Burkholderia fungorum, Burkholderia mallei, Campylobacter jejuni, Chlamydia pneumoniae,*

35   *Chlamydia trachomatis, Clostridium acetobutylicum, Clostridium botulinum, Clostridium difficile, Corynebacterium diptheriae, Enterobacter cloacae, Enterococcus faecium, Haemophilus influenzae, Helicobacter pylori, Legionella pneumophila, Listeria monocytogenes, Moraxella catarrhalis, Mycobacterium avium, Mycobacterium bovis, Mycobacterium leprae, Mycobacterium*

tuberculosis, Mycoplasma genitalium, Mycoplasma pneumoniae, Neisseria gonorrhoeae, Neisseria meningitidis, Pasteurella multocida, Proteus mirabilis, Pseudomonas putida, Pseudomonas syringae, Salmonella paratyphi, Salmonella typhi, Staphylococcus epidermidis, Staphylococcus haemolyticus, Streptococcus mutans, Streptococcus pneumoniae, Streptococcus pyogenes,

5   *Treponema pallidum, Ureaplasma urealyticum, Vibrio cholerae* or *Yersinia pestis* or the genes corresponding thereto, may also be hybridized to a microarray containing the *Escherichia coli, Staphylococcus aureus, Enterococcus faecalis, Klebsiella pneumoniae, Pseudomonas aeruginosa, Salmonella typhimurium, Acinetobacter baumannii, Bacillus anthracis, Bacteroides fragilis, Bordetella pertussis, Borrelia burgdorferi, Burkholderia cepacia, Burkholderia fungorum,*

10 *Burkholderia mallei, Campylobacter jejuni, Chlamydia pneumoniae, Chlamydia trachomatis, Clostridium acetobutylicum, Clostridium botulinum, Clostridium difficile, Corynebacterium diptheriae, Enterobacter cloacae, Enterococcus faecium, Haemophilus influenzae, Helicobacter pylori, Legionella pneumophila, Listeria monocytogenes, Moraxella catarrhalis, Mycobacterium avium, Mycobacterium bovis, Mycobacterium leprae, Mycobacterium tuberculosis, Mycoplasma*

15 *genitalium, Mycoplasma pneumoniae, Neisseria gonorrhoeae, Neisseria meningitidis, Pasteurella multocida, Proteus mirabilis, Pseudomonas putida, Pseudomonas syringae, Salmonella paratyphi, Salmonella typhi, Staphylococcus epidermidis, Staphylococcus haemolyticus, Streptococcus mutans, Streptococcus pneumoniae, Streptococcus pyogenes, Treponema pallidum, Ureaplasma urealyticum, Vibrio cholerae* or *Yersinia pestis* (including the nucleic acids of SEQ ID NOs.: 6214-

20 42397) to gauge the homology between the *Escherichia coli, Staphylococcus aureus, Enterococcus faecalis, Klebsiella pneumoniae, Pseudomonas aeruginosa, Salmonella typhimurium, Acinetobacter baumannii, Bacillus anthracis, Bacteroides fragilis, Bordetella pertussis, Borrelia burgdorferi, Burkholderia cepacia, Burkholderia fungorum, Burkholderia mallei, Campylobacter jejuni, Chlamydia pneumoniae, Chlamydia trachomatis, Clostridium acetobutylicum, Clostridium*

25 *botulinum, Clostridium difficile, Corynebacterium diptheriae, Enterobacter cloacae, Enterococcus faecium, Haemophilus influenzae, Helicobacter pylori, Legionella pneumophila, Listeria monocytogenes, Moraxella catarrhalis, Mycobacterium avium, Mycobacterium bovis, Mycobacterium leprae, Mycobacterium tuberculosis, Mycoplasma genitalium, Mycoplasma pneumoniae, Neisseria gonorrhoeae, Neisseria meningitidis, Pasteurella multocida, Proteus*

30 *mirabilis, Pseudomonas putida, Pseudomonas syringae, Salmonella paratyphi, Salmonella typhi, Staphylococcus epidermidis, Staphylococcus haemolyticus, Streptococcus mutans, Streptococcus pneumoniae, Streptococcus pyogenes, Treponema pallidum, Ureaplasma urealyticum, Vibrio cholerae* or *Yersinia pestis* sequences and the proliferation-required nucleic acids from other cells or microorganisms. For example, the proliferation-required nucleic acid may be from

35 *Acinetobacter baumannii, Anaplasma marginale, Aspergillus fumigatus, Bacillus anthracis, Bacteroides fragilis, Bordetella pertussis, Borrelia burgdorferi, Burkholderia cepacia, Burkholderia fungorum, Burkholderia mallei, Campylobacter jejuni, Candida albicans, Candida glabrata* (also called *Torulopsis glabrata*), *Candida tropicalis, Candida parapsilosis, Candida*

guilliermondii, Candida krusei, Candida kefyr (also called *Candida pseudotropicalis*), *Candida dubliniensis, Chlamydia pneumoniae, Chlamydia trachomatis, Clostridium acetobutylicum, Clostridium botulinum, Clostridium difficile, Clostridium perfringens, Coccidioides immitis, Corynebacterium diptheriae, Cryptococcus neoformans, Enterobacter cloacae, Enterococcus*

5   *faecalis, Enterococcus faecium, Escherichia coli, Haemophilus influenzae, Helicobacter pylori, Histoplasma capsulatum, Klebsiella pneumoniae, Legionella pneumophila, Listeria monocytogenes, Moraxella catarrhalis, Mycobacterium avium, Mycobacterium bovis, Mycobacterium leprae, Mycobacterium tuberculosis, Mycoplasma genitalium, Mycoplasma pneumoniae, Neisseria gonorrhoeae, Neisseria meningitidis, Nocardia asteroides, Pasteurella*

10 *haemolytica, Pasteurella multocida, Pneumocystis carinii, Proteus mirabilis, Proteus vulgaris, Pseudomonas aeruginosa, Pseudomonas putida, Pseudomonas syringae, Salmonella bongori, Salmonella cholerasuis, Salmonella enterica, Salmonella paratyphi, Salmonella typhi, Salmonella typhimurium, Shigella boydii, Shigella dysenteriae, Shigella flexneri, Shigella sonnei, Staphylococcus aureus, Staphylococcus epidermidis, Staphylococcus haemolyticus, Streptococcus*

15 *pneumoniae, Streptococcus mutans, Streptococcus pyogenes, Treponema pallidum, Ureaplasma urealyticum, Vibrio cholerae, Vibrio parahaemolyticus, Vibrio vulnificans, Yersinia enterocolitica, Yersinia pestis* or any species falling within the genera of any of the above species. In some embodiments of the present invention, the proliferation-required nucleotide sequences from *Escherichia coli, Staphylococcus aureus, Enterococcus faecalis, Klebsiella pneumoniae,*

20 *Pseudomonas aeruginosa, Salmonella typhimurium, Acinetobacter baumannii, Bacillus anthracis, Bacteroides fragilis, Bordetella pertussis, Borrelia burgdorferi, Burkholderia cepacia, Burkholderia fungorum, Burkholderia mallei, Campylobacter jejuni, Chlamydia pneumoniae, Chlamydia trachomatis, Clostridium acetobutylicum, Clostridium botulinum, Clostridium difficile, Corynebacterium diptheriae, Enterobacter cloacae, Enterococcus faecium, Haemophilus*

25 *influenzae, Helicobacter pylori, Legionella pneumophila, Listeria monocytogenes, Moraxella catarrhalis, Mycobacterium avium, Mycobacterium bovis, Mycobacterium leprae, Mycobacterium tuberculosis, Mycoplasma genitalium, Mycoplasma pneumoniae, Neisseria gonorrhoeae, Neisseria meningitidis, Pasteurella multocida, Proteus mirabilis, Pseudomonas putida, Pseudomonas syringae, Salmonella paratyphi, Salmonella typhi, Staphylococcus epidermidis, Staphylococcus*

30 *haemolyticus, Streptococcus mutans, Streptococcus pneumoniae, Streptococcus pyogenes, Treponema pallidum, Ureaplasma urealyticum, Vibrio cholerae* or *Yersinia pestis* or homologous nucleic acids are used to identify proliferation-required sequences in an organism other than E. coli. In some embodiments of the present invention, the proliferation-required sequences may be from an organism other than E. coli. The proliferation-required nucleic acids from a cell or microorganism

35 other than *Escherichia coli, Staphylococcus aureus, Enterococcus faecalis, Klebsiella pneumoniae, Pseudomonas aeruginosa, Salmonella typhimurium, Acinetobacter baumannii, Bacillus anthracis, Bacteroides fragilis, Bordetella pertussis, Borrelia burgdorferi, Burkholderia cepacia, Burkholderia fungorum, Burkholderia mallei, Campylobacter jejuni, Chlamydia pneumoniae,*

Chlamydia trachomatis, Clostridium acetobutylicum, Clostridium botulinum, Clostridium difficile, Corynebacterium diptheriae, Enterobacter cloacae, Enterococcus faecium, Haemophilus influenzae, Helicobacter pylori, Legionella pneumophila, Listeria monocytogenes, Moraxella catarrhalis, Mycobacterium avium, Mycobacterium bovis, Mycobacterium leprae, Mycobacterium
5 *tuberculosis, Mycoplasma genitalium, Mycoplasma pneumoniae, Neisseria gonorrhoeae, Neisseria meningitidis, Pasteurella multocida, Proteus mirabilis, Pseudomonas putida, Pseudomonas syringae, Salmonella paratyphi, Salmonella typhi, Staphylococcus epidermidis, Staphylococcus haemolyticus, Streptococcus mutans, Streptococcus pneumoniae, Streptococcus pyogenes, Treponema pallidum, Ureaplasma urealyticum, Vibrio cholerae* or *Yersinia pestis* may be
10 hybridized to the array under a variety of conditions which permit hybridization to occur when the probe has different levels of homology to the nucleotide sequence on the microarray. This would provide an indication of homology across the cells or microorganisms as well as clues to other possible essential genes in these cells or microorganisms.

         In some embodiments of the present invention, the essential gene products described herein
15 are used in methods of identifying a target on which a compound that inhibits cellular proliferation acts. Such methods are described in the U.S. Patent Application entitled METHODS FOR IDENTIFYING THE TARGET OF A COMPOUND WHICH INHIBITS CELLULAR PROLIFERATION, filed February 8, 2002. As employed herein, some embodiments of methods used to identify a target on which a compound that inhibits cellular proliferation acts utilize
20 collections or cultures of strains comprising strains which either overexpress a different gene product which is required for cellular proliferation (such as the gene products described herein) or underexpress a different gene product (such as the gene products described herein) which is required for cellular proliferation (i.e. at least some of the strains in the culture overexpress or underexpress a gene product required for cellular proliferation). In some embodiments, the present
25 invention uses collections or cultures of strains comprising both strains which overexpress gene products required for cellular proliferation and strains which underexpress the same gene products required for cellular proliferation. Preferably, each of the strains present in the culture or collection either overexpresses or underexpresses a different gene product which is required for cellular proliferation (i.e. all of the strains in the culture overexpress or underexpress a gene product
30 required for cellular proliferation). However, in some embodiments, the culture or collection may include one or more strains which do not overexpress or underexpress a gene product which is required for proliferation. The gene product which is overexpressed or underexpressed in each strain may be any gene product which is required for cellular prolifereation, including a gene product whose activity or level is inhibited by a nucleic acid comprising a nucleotide sequence
35 selected from the group consisting of SEQ ID NOs.: 1-6213, a gene product encoded by a nucleic acid comprising a nucleotide sequence selected from the group consisting of SEQ ID NOs.: 6214-42397, a gene product comprising an amino acid sequence selected from the group consisting of SEQ ID NOs.: 42398-78581, a gene product whose activity or level is inhibited by a homologous

antisense nucleic acid, a gene product encoded by a homologous coding nucleic acid, and a gene product comprising a homologous polypeptide.

As used herein the term "culture" refers to a plurality of strains growing in a single aliquot of a liquid growth medium and the term "collection" refers to a plurality of strains each of which is
5   growing in a separate aliquot of liquid growth medium or a different location on a solid growth medium.

In some embodiments, if desired, one or more of the strains in the culture or collection of strains may overexpress or underexpress more than one gene product described herein which is required for cellular proliferation. In this embodiment, the gene products which are overexpressed
10   or underexpressed in one or more of the strains may be functionally related or functionally unrelated. This may facilitate the identification of compounds when two or more gene products share similar functions in the cell or where the cell has multiple biochemical pathways which lead to a particular end product.

Alternatively, if the gene product described herein to be overexpressed or underexpressed is
15   encoded by a gene which is part of an operon containing a plurality of genes, the desired gene may be overexpressed or underexpressed while the remaining genes in the operon are expressed at levels where they do not impact the ability of the cell to grow in the presence of a particular compound. For example, the desired gene may be placed under the control of a regulatable promoter, a transcriptional terminator may be placed 3' of the desired gene and a promoter, preferably a
20   constitutive promoter, may be placed 3' of the transcriptional terminator and 5' of the remaining genes in the operon.

In some embodiments, the culture or collection of strains may comprise a strain which overexpresses or underexpresses a gene product whose activity or level is inhibited by a nucleic acid comprising a nucleotide sequence selected from the group consisting of SEQ ID NOs.: 1-6213.
25   In some embodiments, the culture or collection of strains may comprise strains which in aggregate overexpress or underexpress at least two gene products whose activity or level is inhibited by a nucleic acid selected from the group consisting of SEQ ID NOS.: 1-6213, at least 10 gene products whose activity or level is inhibited by a nucleic acid selected from the group consisting of SEQ ID NOS.: 1-6213, at least 20 gene products whose activity or level is inhibited by a nucleic acid
30   selected from the group consisting of SEQ ID NOS.: 1-6213, at least 30 gene products whose activity or level is inhibited by a nucleic acid selected from the group consisting of SEQ ID NOS.: 1-6213, at least 50 gene products whose activity or level is inhibited by a nucleic acid selected from the group consisting of SEQ ID NOS.: 1-6213, at least 100 gene products whose activity or level is inhibited by a nucleic acid selected from the group consisting of SEQ ID NOS.: 1-6213, at least 300
35   gene products whose activity or level is inhibited by a nucleic acid selected from the group consisting of SEQ ID NOS.: 1-6213 or more than 300 gene products whose activity or level is inhibited by a nucleic acid selected from the group consisting of SEQ ID NOS.: 1-6213, wherein each strain in the culture or collection of strains overexpresses or underexpresses a single gene

product whose activity or level is inhibited by a nucleic acid selected from the group consisting of SEQ ID NOs. 1-6213. Alternatively, if desired, one or more of the strains in the culture or collection of strains may overexpress or underexpress more than one gene product whose activity or level is inhibited by a nucleic acid selected from the group consisting of SEQ ID NOs. 1-6213.

5   In other embodiments, the culture or collection of strains may comprise a strain which overexpresses or underexpresses a gene product encoded by a nucleic acid comprising a nucleotide sequence selected from the group consisting of SEQ ID NOs.: 6214-42397. In some embodiments, the culture or collection of strains may comprise strains which in aggregate overexpress or underexpress at least two gene products encoded by a nucleic acid comprising a nucleotide

10   sequence selected from the group consisting of SEQ ID NOs.: 6214-42397, at least 10 gene products encoded by a nucleic acid comprising a nucleotide sequence selected from the group consisting of SEQ ID NOs.: 6214-42397, at least 20 gene products encoded by a nucleic acid comprising a nucleotide sequence selected from the group consisting of SEQ ID NOs.: 6214-42397, at least 30 gene products encoded by a nucleic acid comprising a nucleotide sequence selected from

15   the group consisting of SEQ ID NOs.: 6214-42397, at least 50 gene products encoded by a nucleic acid comprising a nucleotide sequence selected from the group consisting of SEQ ID NOs.: 6214-42397, at least 100 gene products encoded by a nucleic acid comprising a nucleotide sequence selected from the group consisting of SEQ ID NOs.: 6214-42397, at least 300 gene products encoded by a nucleic acid comprising a nucleotide sequence selected from the group consisting of

20   SEQ ID NOs.: 6214-42397 or more than 300 gene products encoded by a nucleic acid comprising a nucleotide sequence selected from the group consisting of SEQ ID NOs.: 6214-42397, wherein each strain in the culture or collection of strains overexpresses or underexpresses a single gene product encoded by a nucleic acid selected from the group consisting of SEQ ID NOs. 6214-42397. Alternatively, if desired, one or more strains in the culture or collection of strains may overexpress

25   or underexpress more than one gene product encoded by a nucleic acid selected from the group consisting of SEQ ID NOs. 6214-42397.

          In some embodiments the culture or collection of strains comprises a strain in which a gene product comprising an amino acid sequence selected from the group consisting of SEQ ID NOs.: 42938-78581 is overexpressed or underexpressed. In some embodiments, the culture or collection

30   of strains may comprise strains which in aggregate overexpress or underexpress at least two gene products comprising an amino acid sequence selected from the group consisting of SEQ ID NOs.: 42938-78581, at least 10 gene products comprising an amino acid sequence selected from the group consisting of SEQ ID NOs.: 42938-78581, at least 20 gene products comprising an amino acid sequence selected from the group consisting of SEQ ID NOs.: 42938-78581, at least 30 gene

35   products comprising an amino acid sequence selected from the group consisting of SEQ ID NOs.: 42938-78581, at least 50 gene products comprising an amino acid sequence selected from the group consisting of SEQ ID NOs.: 42938-78581, at least 100 gene products comprising an amino acid sequence selected from the group consisting of SEQ ID NOs.: 42938-78581, at least 300 gene

products comprising an amino acid sequence selected from the group consisting of SEQ ID NOs.: 42938-78581 or more than 300 gene products comprising an amino acid sequence selected from the group consisting of SEQ ID NOs.: 42938-78581, wherein each strain in the culture or collection of strains overexpresses or underexpresses a single gene product selected from the group consisting of

5   SEQ ID NOs. 42938-78581. Alternatively, if desired one or more of the strains in the culture or collection of strains may overexpress or underexpress more than one gene product selected from the group consisting of SEQ ID NOs. 42938-78581.

In other embodiments, the culture or collection of strains comprises a strain in which at least one of the gene products encoded by a homologous coding nucleic acid as defined above is

10   overexpressed or underexpressed. In some embodiments, the culture or collection of strains may comprise strains which in aggregate overexpress or underexpress at least 2, at least 10, at least 20, at least 30, at least 50, at least 100, at least 300 or more than 300 gene products encoded by a homologous coding nucleic acid as defined above. If desired the culture or collection of strains may comprise one or more strains which overexpress or underexpress more than one gene product

15   encoded by a homologous coding nucleic acid. In further embodiments, the culture or collection of strains comprises a strain in which at least one, at least 10, at least 20, at least 30, at least 50, at least 100, at least 300 or more than 300 homologous polypeptides as defined above is overexpressed or underexpressed. If desired the culture or collection of strains may comprise one or more strains which overexpress or underexpress more than one homologous polypeptide.

20   For example, in some embodiments, the culture or collection of strains comprises a strain in which at least one gene product selected from the group consisting of a gene product having at least 70% nucleotide sequence identity as determined using BLASTN version 2.0 with the default parameters to a gene product whose expression is inhibited by an antisense nucleic acid comprising a nucleotide sequence selected from the group consisting of SEQ ID NOs.: 1-6213, a gene product

25   encoded by a nucleic acid having at least 70% nucleotide sequence identity as determined using BLASTN version 2.0 with the default parameters to a nucleic acid encoding a gene product whose expression is inhibited by an antisense nucleic acid comprising a nucleotide sequence selected from the group consisting of SEQ ID NOs: 1-6213, a gene product having at least 25% amino acid identity as determined using FASTA version 3.0t78 with the default parameters to a gene product

30   whose expression is inhibited by an antisense nucleic acid comprising a nucleotide sequence selected from the group consisting of SEQ ID NOs.: 1-6213, a gene product encoded by a nucleic acid which hybridizes to a nucleic acid comprising a nucleotide sequence selected from the group consisting of SEQ ID NOs.: 1-6213 under stringent conditions, a gene product encoded by a nucleic acid which hybridizes to a nucleic acid comprising a nucleotide sequence selected from the group

35   consisting of SEQ ID NOs.: 1-6213 under moderate conditions, and a gene product whose activity may be complemented by the gene product whose activity is inhibited by a nucleic acid comprising a nucleotide sequence selected from the group consisting of SEQ ID NOs: 1-6213 is overexpressed or underexpressed, wherein each strain overexpresses or underexpresses one gene product. In some

embodiments, the culture or collection of strains may comprise strains in which in aggregate at least 2, at least 10, at least 20, at least 30, at least 50, at least 100, at least 300, or more than 300 gene products selected from the group consisting of a gene product having at least 70% nucleotide sequence identity as determined using BLASTN version 2.0 with the default parameters to a gene

5   product whose expression is inhibited by an antisense nucleic acid comprising a nucleotide sequence selected from the group consisting of SEQ ID NOs.: 1-6213, a gene product encoded by a nucleic acid having at least 70% nucleotide sequence identity as determined using BLASTN version 2.0 with the default parameters to a nucleic acid encoding a gene product whose expression is inhibited by an antisense nucleic acid comprising a nucleotide sequence selected from the group

10   consisting of SEQ ID NOs: 1-6213, a gene product having at least 25% amino acid identity as determined using FASTA version 3.0t78 with the default parameters to a gene product whose expression is inhibited by an antisense nucleic acid comprising a nucleotide sequence selected from the group consisting of SEQ ID NOs.: 1-6213, a gene product encoded by a nucleic acid which hybridizes to a nucleic acid comprising a nucleotide sequence selected from the group consisting of

15   SEQ ID NOs.: 1-6213 under stringent conditions, a gene product encoded by a nucleic acid which hybridizes to a nucleic acid comprising a nucleotide sequence selected from the group consisting of SEQ ID NOs.: 1-6213 under moderate conditions, and a gene product whose activity may be complemented by the gene product whose activity is inhibited by a nucleic acid comprising a nucleotide sequence selected from the group consisting of SEQ ID NOs: 1-6213 is overexpressed

20   or underexpressed, wherein each strain overexpresses or underexpresses one gene product.

If desired, one or more of the strains in the culture or collection of strains may overexpress or underexpress more than one gene product selected from the group consisting of a gene product having at least 70% nucleotide sequence identity as determined using BLASTN version 2.0 with the default parameters to a gene product whose expression is inhibited by an antisense nucleic acid

25   comprising a nucleotide sequence selected from the group consisting of SEQ ID NOs.: 1-6213, a gene product encoded by a nucleic acid having at least 70% nucleotide sequence identity as determined using BLASTN version 2.0 with the default parameters to a nucleic acid encoding a gene product whose expression is inhibited by an antisense nucleic acid comprising a nucleotide sequence selected from the group consisting of SEQ ID NOs: 1-6213, a gene product having at least

30   25% amino acid identity as determined using FASTA version 3.0t78 with the default parameters to a gene product whose expression is inhibited by an antisense nucleic acid comprising a nucleotide sequence selected from the group consisting of SEQ ID NOs.: 1-6213, a gene product encoded by a nucleic acid which hybridizes to a nucleic acid comprising a nucleotide sequence selected from the group consisting of SEQ ID NOs.: 1-6213 under stringent conditions, a gene product encoded by a

35   nucleic acid which hybridizes to a nucleic acid comprising a nucleotide sequence selected from the group consisting of SEQ ID NOs.: 1-6213 under moderate conditions, and a gene product whose activity may be complemented by the gene product whose activity is inhibited by a nucleic acid comprising a nucleotide sequence selected from the group consisting of SEQ ID NOs: 1-6213.

In further embodiments, the culture or collection of strains comprises a strain in which at least one gene product encoded by a nucleic acid comprising a nucleotide sequence selected from the group consisting of a nucleic acid comprising a nucleic acid having at least 70% nucleotide sequence identity as determined using BLASTN version 2.0 with the default parameters to a

5 nucleotide sequence selected from the group consisting of SEQ ID NOS.: 6214-42397, a nucleic acid comprising a nucleotide sequence which hybridizes to a sequence selected from the group consisting of SEQ ID NOS.: 6214-42397 under stringent conditions, and a nucleic acid comprising a nucleotide sequence which hybridizes to a nucleotide sequence selected from the group consisting of SEQ ID NOS.: 6214-42397 under moderate conditions is overexpressed or underexpressed,

10 wherein each strain overexpresses or underexpresses one gene product. In some embodiments, the culture or collection of strains comprises a strain or a group of strains in which in aggregate at least 2, at least 10, at least 20, at least 30, at least 50, at least 100, at least 300, or more than 300 gene products encoded by a nucleic acid comprising a nucleotide sequence selected from the group consisting of a nucleic acid comprising a nucleic acid having at least 70% nucleotide sequence

15 identity as determined using BLASTN version 2.0 with the default parameters to a nucleotide sequence selected from the group consisting of SEQ ID NOS.: 6214-42397, a nucleic acid comprising a nucleotide sequence which hybridizes to a sequence selected from the group consisting of SEQ ID NOS.: 6214-42397 under stringent conditions, and a nucleic acid comprising a nucleotide sequence which hybridizes to a nucleotide sequence selected from the group consisting

20 of SEQ ID NOS.: 6214-42397 under moderate conditions is overexpressed or underexpressed, wherein each strain overexpresses or underexpresses one gene product.

If desired, one or more of the strains in the culture or collection of strains may overexpress or underexpress more than one gene product encoded by a nucleic acid comprising a nucleotide sequence selected from the group consisting of a nucleic acid comprising a nucleic acid having at

25 least 70% nucleotide sequence identity as determined using BLASTN version 2.0 with the default parameters to a nucleotide sequence selected from the group consisting of SEQ ID NOS.: 6214-42397, a nucleic acid comprising a nucleotide sequence which hybridizes to a sequence selected from the group consisting of SEQ ID NOS.: 6214-42397 under stringent conditions, and a nucleic acid comprising a nucleotide sequence which hybridizes to a nucleotide sequence selected from the

30 group consisting of SEQ ID NOS.: 6214-42397 under moderate conditions.

In additional embodiments, the culture or collection of strains comprises a strain in which at least one gene product comprising a polypeptide selected from the group consisting of a polypeptide having at least 25% amino acid identity as determined using FASTA version 3.0t78 to a polypeptide selected from the group consisting of SEQ ID NOs.: 42938-78581 and a polypeptide

35 whose activity may be complemented by a polypeptide selected from the group consisting of SEQ ID NOs: 42938-78581 is overexpressed or underexpressed, wherein each strain overexpresses or underexpresses one gene product. In some embodiments, the culture or collection of strains comprises a strain or a group of strains in which in aggregate at least 2, at least 10, at least 20, at

least 30, at least 50, at least 100, at least 300, or more than 300 gene products comprising a polypeptide selected from the group consisting of a polypeptide having at least 25% amino acid identity as determined using FASTA version 3.0t78 to a polypeptide selected from the group consisting of SEQ ID NOs.: 42938-78581 and a polypeptide whose activity may be complemented

5   by a polypeptide selected from the group consisting of SEQ ID NOs: 42938-78581 is overexpressed or underexpressed, wherein each strain overexpresses or underexpresses one gene product.

If desired, one or more of the strains in the culture or collection of strains may overexpress or underexpress more than one polypeptide selected from the group consisting of a polypeptide having at least 25% amino acid identity as determined using FASTA version 3.0t78 to a

10   polypeptide selected from the group consisting of SEQ ID NOs.: 42938-78581 and a polypeptide whose activity may be complemented by a polypeptide selected from the group consisting of SEQ ID NOs: 42938-78581.

The methods of the present invention may be used to identify the targets of compounds which inhibit the proliferation of any desired cell or organism. In some embodiments, these

15   methods are employed to identify the targets of compounds which inhibit the proliferation of bacteria, fungi, or protozoans. In further embodiments, these methods are employed to identify the targets of compounds which inhibit the growth of an organism selected from the group consisting of *Acinetobacter baumannii, Anaplasma marginale, Aspergillus fumigatus, Bacillus anthracis, Bacteroides fragilis, Bordetella pertussis, Borrelia burgdorferi, Burkholderia cepacia,*

20   *Burkholderia fungorum, Burkholderia mallei, Campylobacter jejuni, Candida albicans, Candida glabrata* (also called *Torulopsis glabrata*), *Candida tropicalis, Candida parapsilosis, Candida guilliermondii, Candida krusei, Candida kefyr* (also called *Candida pseudotropicalis*), *Candida dubliniensis, Chlamydia pneumoniae, Chlamydia trachomatis, Clostridium acetobutylicum, Clostridium botulinum, Clostridium difficile, Clostridium perfringens, Coccidioides immitis,*

25   *Corynebacterium diptheriae, Cryptococcus neoformans, Enterobacter cloacae, Enterococcus faecalis, Enterococcus faecium, Escherichia coli, Haemophilus influenzae, Helicobacter pylori, Histoplasma capsulatum, Klebsiella pneumoniae, Legionella pneumophila, Listeria monocytogenes, Moraxella catarrhalis, Mycobacterium avium, Mycobacterium bovis, Mycobacterium leprae, Mycobacterium tuberculosis, Mycoplasma genitalium, Mycoplasma*

30   *pneumoniae, Neisseria gonorrhoeae, Neisseria meningitidis, Nocardia asteroides, Pasteurella haemolytica, Pasteurella multocida, Pneumocystis carinii, Proteus mirabilis, Proteus vulgaris, Pseudomonas aeruginosa, Pseudomonas putida, Pseudomonas syringae, Salmonella bongori, Salmonella cholerasuis, Salmonella enterica, Salmonella paratyphi, Salmonella typhi, Salmonella typhimurium, Shigella boydii, Shigella dysenteriae, Shigella flexneri, Shigella sonnei,*

35   *Staphylococcus aureus, Staphylococcus epidermidis, Staphylococcus haemolyticus, Streptococcus pneumoniae, Streptococcus mutans, Streptococcus pyogenes, Treponema pallidum, Ureaplasma urealyticum, Vibrio cholerae, Vibrio parahaemolyticus, Vibrio vulnificans, Yersinia enterocolitica, Yersinia pestis* or any species falling within the genera of any of the above species.

Overexpression may be obtained using a variety of techniques familiar to those skilled in the art. For example, overexpression may be obtained by operably linking a gene encoding a gene product whose activity or level is inhibited by a nucleic acid comprising a nucleotide sequence selected from the group consisting of SEQ ID NOs.: 1-6213, a gene product encoded by a nucleic

5   acid comprising a nucleotide sequence selected from the group consisting of SEQ ID NOs.: 6214-42397, a gene product comprising an amino acid sequence selected from the group consisting of SEQ ID NOs.: 42398-78581, a gene product whose activity or level is inhibited by a homologous antisense nucleic acid, a gene product encoded by a homologous coding nucleic acid, or a gene product comprising a homologous polypeptide to a promoter which transcribes a higher level of

10   mRNA encoding or comprising the gene product than does a wild type cell.

A variety of promoters may be used to overexpress the gene product described herein, including a gene product whose activity or level is inhibited by a nucleic acid comprising a nucleotide sequence selected from the group consisting of SEQ ID NOs.: 1-6213, a gene product encoded by a nucleic acid comprising a nucleotide sequence selected from the group consisting of

15   SEQ ID NOs.: 6214-42397, a gene product comprising an amino acid sequence selected from the group consisting of SEQ ID NOs.: 42398-78581, a gene product whose activity or level is inhibited by a homologous antisense nucleic acid, a gene product encoded by a homologous coding nucleic acid, and a gene product comprising a homologous polypeptide. The promoters used to overexpress the gene product may be relatively strong promoters, promoters which possess a moderate level of

20   activity, or relatively weak promoters and may be either constitutive or regulatable promoters. In some embodiments, several strains, each of which overexpresses the gene product to a different extent, may be used in order to optimize the degree of overexpression of the gene product.

In some embodiments, each of the gene products required for proliferation may be placed under the control of several different promoters of varying strengths to create several different

25   strains which express the gene product at varying levels. The level of expression of the gene product in each of the strains is compared to that in wild type cells in order to identify a promoter which provides a desired level of expression relative to wild type cells (i.e. a desired level of overexpression or underexpression). The strain having the desired level of expression is then included in a culture or collection of strains to be contacted with a test compound as discussed

30   below. Examples of suites of regulatable promoters having varying strengths that are useful for the expression of gene products at varying levels are described in U.S. Patent Application Serial Number 10/032,393, filed on December 21, 2002.

The promoter is selected to be active in the type of cell in which the gene product is to be expressed. For example, for overexpression of the gene product in mammalian cells, the gene

35   encoding the gene product may be operably linked to promoters such as the SV40 promoter, the metallothionine promoter, the MMTV promoter, the RSV promoter, the tetP promoter, the adenovirus major late promoter or other promoters known to those skilled in the art. In yeast, the gene encoding the gene product may be operably linked to promoters such as the CYC1, ADHI,

ADHII, GAL1, GAL10, PHO5, PGK or other promoters used in the art. Similarly, in bacteria, the gene encoding the gene product may be operably linked to the , SP6, T3, trc promoter, lac promoter, temperature regulated lambda promoters, the *Bacillus* aprE and nprE promoters (U.S. Patent No. 5,387,521), the bacteriophage lambda P_L and P_R promoters (Renaut, et al., (1981) Gene

5   15: 81) the trp promoter (Russell, et al., (1982) Gene 20: 23), the tac promoter (de Boer et al., (1983) Proc. Natl. Acad. Sci. USA 80: 21), *B. subtilis* alkaline protease promoter (Stahl et al, (1984) J. Bacteriol. 158, 411-418) alpha amylase promoter of *B. subtilis* (Yang et al., (1983) Nucleic Acids Res. 11, 237-249) or *B. amyloliquefaciens* (Tarkinen, et al, (1983) J. Biol. Chem. 258, 1007-1013), the neutral protease promoter from *B. subtilis* (Yang et al, (1984) J. Bacteriol.

10   160, 15-21), T7 RNA polymerase promoter (Studier and Moffatt (1986) J Mol Biol. 189(1):113-30), *B. subtilis xyl* promoter or mutant tetR promoter active in bacilli (Geissendorfer & Hillen (1990) Appl. Microbiol. Biotechnol. 33:657-663), Staphylococcal enterotoxin D promoter (Zhang and Stewart (2000) J. Bacteriol. 182(8):2321-5), cap8 operon promoter from *Staphylococcus aureus* (Ouyang et al., (1999) J. Bacteriol. 181(8):2492-500), the lactococcal nisA promoter (Eichenbaum

15   (1998) Appl Environ Microbiol. 64(8):2763-9), promoters from in *Acholeplasma laidlawii* (Jarhede et al., (1995) Microbiology 141 (Pt 9):2071-9), porA promoter of *Neisseria meningitidis* (Sawaya et al., (1999) Gene 233:49-57), the fbpA promoter of *Neisseria gonorrhoeae* (Forng et al., (1997) J. Bacteriol. 179:3047-3052), *Corynebacterium diphtheriae* toxin gene promoter (Schmitt and Holmes (1994) J. Bacteriol. 176(4):1141-9), the hasA operon promoter from Group A Streptococci (Alberti

20   et al., (1998) Mol Microbiol 28(2):343-53), the rpoS promoter of *Pseudomonas putida* (Kojic and Venturi (2001) J. Bacteriol. 183:3712-3720), the *Acinetobacter baumannii* phosphate regulated *ppk* gene promoter (Gavigan et al., Microbiology 145:2931-7 (1999)); the *Acinetobacter baumannii* *adhC1* promoter which is induced under iron limitation and repressed when the cells are cultured in the presence of free inorganic iron (Echenique et al., Microbiology 147:2805-15 (2001)); the *flaB*

25   promoter of pGK12 active in *Borrelia burgdorferi* (Sartakova et al., Proc Natl Acad Sci U S A. 97(9):4850-5 (2000)); the use of Ptrc promoter results in strong inducer-dependent expression in *Burkholderia spp* (Santos et al., FEMS Microbiol Lett 195(1):91-6 (2001)); the iron regulated *sodA* promoter of *Bordetella pertussis* (Graeff-Wohlleben et al., J Bacteriol 179(7):2194-201 (1997)); UV-inducible bcn and uviAB promoters in *Clostrdia spp* (Garnier and Cole Mol Microbiol

30   2(5):607-14 (1988)); the heat-inducible *clpB* promoter of *Campylobacter jejuni* (Thies et al., Gene 230(1):61-7 (1999)); promoters carrying bacteriophage C1 operator sites in *Klebsiella pneumoniae* (Schoefield et al, J Bacteriol 183(23):6947-50 (2001)); the *Proteus mirabilis* ureR promoter (Poore et al., J Bacteriol 183(15):4526-35 (2001)); and the heat-inducible groESL promoter in *Listeria monocytogenes*, and the IPTG inducible promoter in pLEX5BA (Krause et al., J. Mol. Biol. 274:

35   365 (1997). In another embodiment, which may be useful in *Staphylococcus aureus*, the promoter is a novel inducible promoter system, XylT5, comprising a modified T5 promoter fused to the *xylO* operator from the *xylA* promoter of *Staphylococcus aureus*. This promoter is described in U.S. Patent Application Serial Number 10/032,393. In another embodiment the promoter may be a two-

component inducible promoter system in which the T7 RNA polymerase gene is integrated on the chromosome and is regulated by *lac*UV5/ *lac*O (Brunschwig, E. and Darzins, A. 1992. Gene 111:35-41, and a T7 gene 10 promoter, which is transcribed by T7 RNA polymerase, is fused with a *lac*O operator. In another embodiment the promoter may be the promoters from the plasmids

5   pEPEF3 or pEPEF14, which harbor xylose inducible promoters functional in *E. faecalis*, described in U.S. Patent Application Serial No. 10/032,393. Other promoters which may be used are familiar to those skilled in the art. In fungi, the gene encoding the gene product may be operably linked to the CaACT1 promoter (Morschhauser, Mol. Gen. Genet. 257: 412-420 (1998), or other promoters familiar to those skilled in the art. It will appreciated that other combinations of organisms and

10   promoters may also be used in the present invention.

In some embodiments, overexpression may be achieved by using homologous recombination to replace the natural promoter which drives expression of the proliferation-required genes described herein with a regulatable promoter. For example, the methods described in U.S. Patent Application 09/948,993 may be used to place the gene required for proliferation under the

15   control of a regulatable promoter. Examples of gene products, which are encoded by genes that can be overexpressed by regulatable promoters introduced by such promoter replacement methods include a gene product whose activity or level is inhibited by a nucleic acid comprising a nucleotide sequence selected from the group consisting of SEQ ID NOs.: 1-6213, a gene product encoded by a nucleic acid comprising a nucleotide sequence selected from the group consisting of SEQ ID NOs.:

20   6214-42397, a gene product comprising an amino acid sequence selected from the group consisting of SEQ ID NOs.: 42398-78581, a gene product whose activity or level is inhibited by a homologous antisense nucleic acid, a gene product encoded by a homologous coding nucleic acid, and a gene product comprising a homologous polypeptide.

Briefly, in some embodiments of these methods in which natural promoters are replaced by

25   regulatable promoters, the cells may be haploid, such as bacterial cells. Regulatable promoters that are useful for promoter replacement in bacterial cells include, but are not limited to, the promoters described in U.S. Patent Application Serial Number 10/032,393 filed December 21, 2001. A linear promoter replacement cassette comprising a regulatable promoter flanked by nucleotide sequences having homology to the natural promoter is introduced into the cell. In some embodiments, the

30   cassette also comprises a nucleotide sequence encoding a selectable marker or a marker whose expression is readily identified. The cassette may be a double stranded nucleic acid or a single stranded nucleic acid as described in U.S. Patent Application Serial Number 09/948,993. Upon homologous recombination, the natural promoter is replaced with the regulatable promoter, leaving the gene required for proliferation under the control of the regulatable promoter. Strains in which

35   the gene required for proliferation is under control of the regulatable promoter are grown under conditions in which the regulatable promoter provides a level of the proliferation-required gene product which is above the level in a wild type cell. For example, the strains may be grown in the

presence of an inducer which induces expression from the regulatable promoter, or under conditions in which the action of a repressor on the regulatable promoter is reduced or eliminated.

Alternatively, rather than replacing the native promoters of each of the genes encoding a proliferation-required gene product described herein with a single desired replacement promoter, a
5   plurality of replacement promoters which provide desired expression levels for the gene products to be overexpressed or underexpressed are used. The method is performed as described above except that rather than using a single labeled primer complementary to a nucleotide sequence within the single replacement promoter, a plurality of labeled primers complementary to suitable nucleotide sequences in the plurality of replacement promoters are used.

10   Alternatively, in embodiments in which the level or activity of proliferation-required gene products described herein is reduced by transcribing an antisense nucleic acid complementary to at least a portion of the genes encoding such gene products, the strains may be designed such that the length of the nucleotide sequence encoding the antisense nucleic acid is different for each gene. Amplification reactions are performed as described above using primers at each end of the gene
15   encoding the antisense nucleic acid such that the amplification product corresponding to each gene has a unique length or a dye which allows it to be distinguished from other amplification products of the same length. Alternatively, the lengths of the nucleotide sequences encoding the antisense nucleic acids may not be unique for each gene, but the primers used in the amplification reaction may be selected such that the length of the amplification product corresponding to each gene is
20   unique.

In another embodiment, the native promoters may be replaced with promoters which include therein or adjacent thereto a unique nucleotide sequence which is distinct from that present in the other replacement promoters in the strains in the culture or collection of strains. In this embodiment, each promoter includes or has adjacent thereto a unique "tag" which may be used to
25   identify strains which proliferate more rapidly or more slowly in the culture or collection of strains. The tag may be detected using hybridization based methods or amplification based methods, including the amplification method which generates amplification products having a unique size for each proliferation required gene described above.

Alternatively, the native promoter which directs the transcription of the proliferation-
30   required genes described herein may rendered regulatable by inserting a regulatory element into the chromosome of the cell via homologous recombination such that the regulatory element regulates the level of transcription from the promoter. Examples of gene products, which are encoded by genes that have promoters which can be rendered regulatable by regulatory elements inserted by such methods include a gene product whose activity or level is inhibited by a nucleic acid
35   comprising a nucleotide sequence selected from the group consisting of SEQ ID NOs.: 1-6213, a gene product encoded by a nucleic acid comprising a nucleotide sequence selected from the group consisting of SEQ ID NOs.: 6214-42397, a gene product comprising an amino acid sequence selected from the group consisting of SEQ ID NOs.: 42398-78581, a gene product whose activity or

level is inhibited by a homologous antisense nucleic acid, a gene product encoded by a homologous coding nucleic acid, and a gene product comprising a homologous polypeptide.

A variety of regulatory elements may be used to regulate the expression of essential gene products described herein. The regulatory element may be an operator which is recognized by a

5   repressor (e.g. lac, tet, araBAD repressors) or a nucleotide sequence which is recognized by a transcriptional activator. In some embodiments, the regulatory element may be a transcriptional terminator, a nucleotide sequence which introduces a bend in the DNA or an upstream activating sequence. A linear regulatory element insertion cassette comprising a regulatory element flanked by nucleotide sequences having homology to the natural promoter is introduced into the cell. In

10 some embodiments, the cassette also comprises a nucleotide sequence encoding a selectable marker or a marker whose expression is readily identified. The cassette may be a double stranded nucleic acid or a single stranded nucleic acid as described in U.S. Patent Application Serial Number 09/948,993. Upon homologous recombination, the regulatory element is inserted into the chromosome, leaving the gene required for proliferation under the control of the regulatory

15 element. Strains in which the gene required for proliferation is under control of the regulatory element are grown under conditions in which the regulatable promoter provides a level of the proliferation-required gene product which is above the level in a wild type cell. For example, the strains may be grown in the presence of an inducer which induces expression from the promoter, or under conditions in which the action of a repressor on the promoter is reduced or eliminated. It will

20 be appreciated that the amplification method which generates amplification products having a unique size for each proliferation required gene may be used to detect strains which are overrepresented or underrepresented in the culture or collection of strains. For example, if desired, primers complementary to a nucleotide sequence within the regulatory element may be used in the amplification reaction.

25 The promoter replacement cassette or regulatory element insertion cassette may be a double stranded nucleic acid, such as an amplicon generated through PCR or other amplification methods, or a single stranded nucleic acid, such as an oligonucleotide. For example, single stranded nucleic acids may be introduced into the chromosome using the methods described in Ellis et al., PNAS 98: 6742-6746, 2001.

30 In some embodiments, the cell into which the promoter replacement cassette or regulatory element insertion cassette is introduced has an enhanced frequency of recombination. For example, the cells may lack or have a reduced level or activity of one or more exonucleases which would ordinarily degrade the DNA to be inserted into the chromosome. In further embodiments, the cells may both lack or have reduced levels of exonucleases and express or overexpress proteins involved

35 in mediating homologous recombination. For example, if the methods are performed in *Escherichia coli* or other enteric prokaryotes, cells in which the activity of exonuclease V of the RecBCD recombination pathway, which degrades linear nucleic acids, has been reduced or eliminated, such as recB, recC, or recD mutants may be used. In some embodiments, the cells have

mutations in more than one of the recB, recC, and recD genes which enhance the frequency of homologous recombination. For example the cells may have mutations in both the recB and recC genes.

5   The promoter replacement or regulatory element insertion methods may also be performed in *Escherichia coli* cells in which the activity of the RecET recombinase system of the Rac prophage has been activated, such as cells which carry an sbcA mutation. The RecE gene of the rac prophage encodes ExoVIII a 5'-3' exonuclease, while the RecT gene of the Rac prophage encodes a single stranded DNA binding protein which facilitates renaturation and D-loop formation. Thus, the gene products of the RecE and RecT genes or proteins with analogous functions facilitate

10   homologous recombination. The RecE and RecT genes lie in the same operon but are normally not expressed. However, sbcA mutants activate the expression the RecE and RecT genes. In some embodiments, the methods may be performed in cells which carry mutations in the recB and recC genes as well as the sbcA mutation. The RecE and RecT gene may be constitutively or conditionally expressed. For example, the methods may be performed in *E. coli* strain JC8679,

15   which carries the sbcA23, recB21 and recC22 mutations.

      In some embodiments, the methods may be performed in *Escherichia coli* cells in which recombination via the RecF pathway has been enhanced, such as cells which carry an sbcB mutation.

      It will be appreciated that the RecE and RecT gene products, or proteins with analogous functions may be conditionally or constitutively expressed in prokaryotic organisms other than *E.*

20   *coli*. In some embodiments, these proteins may be conditionally or constitutively expressed in *Acinetobacter baumannii, Anaplasma marginale, Aspergillus fumigatus, Bacillus anthracis, Bacteroides fragilis, Bordetella pertussis, Borrelia burgdorferi, Burkholderia cepacia, Burkholderia fungorum, Burkholderia mallei, Campylobacter jejuni, Candida albicans, Candida*

25   *glabrata* (also called *Torulopsis glabrata*), *Candida tropicalis, Candida parapsilosis, Candida guilliermondii, Candida krusei, Candida kefyr* (also called *Candida pseudotropicalis*), *Candida dubliniensis, Chlamydia pneumoniae, Chlamydia trachomatis, Clostridium acetobutylicum, Clostridium botulinum, Clostridium difficile, Clostridium perfringens, Coccidioides immitis, Corynebacterium diptheriae, Cryptococcus neoformans, Enterobacter cloacae, Enterococcus*

30   *faecalis, Enterococcus faecium, Escherichia coli, Haemophilus influenzae, Helicobacter pylori, Histoplasma capsulatum, Klebsiella pneumoniae, Legionella pneumophila, Listeria monocytogenes, Moraxella catarrhalis, Mycobacterium avium, Mycobacterium bovis, Mycobacterium leprae, Mycobacterium tuberculosis, Mycoplasma genitalium, Mycoplasma pneumoniae, Neisseria gonorrhoeae, Neisseria meningitidis, Nocardia asteroides, Pasteurella*

35   *haemolytica, Pasteurella multocida, Pneumocystis carinii, Proteus mirabilis, Proteus vulgaris, Pseudomonas aeruginosa, Pseudomonas putida, Pseudomonas syringae, Salmonella bongori, Salmonella cholerasuis, Salmonella enterica, Salmonella paratyphi, Salmonella typhi, Salmonella typhimurium, Shigella boydii, Shigella dysenteriae, Shigella flexneri, Shigella sonnei,*

Staphylococcus aureus, Staphylococcus epidermidis, Staphylococcus haemolyticus, Streptococcus pneumoniae, Streptococcus mutans, Streptococcus pyogenes, Treponema pallidum, Ureaplasma urealyticum, Vibrio cholerae, Vibrio parahaemolyticus, Vibrio vulnificans, Yersinia enterocolitica, Yersinia pestis or any species falling within the genera of any of the above species. For example,

5   plasmids encoding these gene products may be introduced into the organism. If desired, the coding sequences encoding these gene products may be optimized to reflect the codon preferences of the organism in which they are to be expressed. Similarly, in some embodiments, the organism may contain mutations analogous to the recB, recC, recD, sbcA or sbcB mutations which enhance the frequency of homologous recombination.

10   In further embodiments, the promoter replacement or regulatory element insertion methods may be conducted in cells which utilize the Red system of bacteriophage lambda (λ) or analogous systems from other phages to enhance the frequency of homologous recombination. The Red system contains three genes, (γ, β and *exo* whose products are the Gam, Bet and Exo proteins (see Ellis et al. PNAS 98:6742-6746, 2001. The Gam protein inhibits the RecBCD exonuclease V, thus

15   permitting Beta and Exo to gain access to the ends of the DNA to be integrated and facilitating homologous recombination. The Beta protein is a single stranded DNA binding protein that promotes the annealing of a single stranded nucleic acid to a complementary single stranded nucleic acid and mediates strand exchange. The Exo protein is a double-stranded DNA dependent 5'-3' exonuclease that leaves 3' overhangs that can act as substrates for recombination. Thus,

20   constitutive or conditional expression of the λ Red proteins or proteins having analogous functions facilitates homologous recombination.

           It will be appreciated that the λ Beta, Gam and Exo proteins, or proteins with analagous functions may be expressed constitutively or conditionally in prokaryotic organisms other than *E. coli*. In some embodiments, these proteins may be conditionally or constitutively expressed in

25   *Acinetobacter baumannii, Anaplasma marginale, Aspergillus fumigatus, Bacillus anthracis, Bacteroides fragilis, Bordetella pertussis, Borrelia burgdorferi, Burkholderia cepacia, Burkholderia fungorum, Burkholderia mallei, Campylobacter jejuni, Candida albicans, Candida glabrata* (also called *Torulopsis glabrata*), *Candida tropicalis, Candida parapsilosis, Candida guilliermondii, Candida krusei, Candida kefyr* (also called *Candida pseudotropicalis*), *Candida*

30   *dubliniensis, Chlamydia pneumoniae, Chlamydia trachomatis, Clostridium acetobutylicum, Clostridium botulinum, Clostridium difficile, Clostridium perfringens, Coccidioides immitis, Corynebacterium diptheriae, Cryptococcus neoformans, Enterobacter cloacae, Enterococcus faecalis, Enterococcus faecium, Escherichia coli, Haemophilus influenzae, Helicobacter pylori, Histoplasma capsulatum, Klebsiella pneumoniae, Legionella pneumophila, Listeria*

35   *monocytogenes, Moraxella catarrhalis, Mycobacterium avium, Mycobacterium bovis, Mycobacterium leprae, Mycobacterium tuberculosis, Mycoplasma genitalium, Mycoplasma pneumoniae, Neisseria gonorrhoeae, Neisseria meningitidis, Nocardia asteroides, Pasteurella haemolytica, Pasteurella multocida, Pneumocystis carinii, Proteus mirabilis, Proteus vulgaris,*

Pseudomonas aeruginosa, Pseudomonas putida, Pseudomonas syringae, Salmonella bongori, Salmonella cholerasuis, Salmonella enterica, Salmonella paratyphi, Salmonella typhi, Salmonella typhimurium, Shigella boydii, Shigella dysenteriae, Shigella flexneri, Shigella sonnei, Staphylococcus aureus, Staphylococcus epidermidis, Staphylococcus haemolyticus, Streptococcus

5 *pneumoniae, Streptococcus mutans, Streptococcus pyogenes, Treponema pallidum, Ureaplasma urealyticum, Vibrio cholerae, Vibrio parahaemolyticus, Vibrio vulnificans, Yersinia enterocolitica, Yersinia pestis* or any species falling within the genera of any of the above species. For example, plasmids encoding these gene products may be introduced into the organism. If desired, the coding sequences encoding these gene products may be optimized to reflect the codon preferences of the

10 organism in which they are to be expressed.

In some embodiments, the cells may have an increased frequency of homologous recombination as a result of more than one of the aforementioned characteristics. In some embodiments, the enhanced frequency of recombination may be a conditional characteristic of the cells which depends on the culture conditions in which the cells are grown. For example, in some

15 embodiments, expression of the λ Red Gam, Exo, and Beta proteins or recE and recT proteins may be regulated. Thus, the cells may have an increased frequency of homologous recombination as a result of any combination of the aforementioned characteristics. For example, in some embodiments, the cell may carry the sbcA and recBC mutations.

In some embodiments, a linear double stranded DNA to be inserted into the chromosome of

20 the organism is introduced into an organism constitutively or conditionally expressing the recE and recT or the λ Beta, Gam and Exo proteins or proteins with analogous functions as described above. In some embodiments, the organism may be *Acinetobacter baumannii, Anaplasma marginale, Aspergillus fumigatus, Bacillus anthracis, Bacteroides fragilis, Bordetella pertussis, Borrelia burgdorferi, Burkholderia cepacia, Burkholderia fungorum, Burkholderia mallei, Campylobacter*

25 *jejuni, Candida albicans, Candida glabrata* (also called *Torulopsis glabrata*), *Candida tropicalis, Candida parapsilosis, Candida guilliermondii, Candida krusei, Candida kefyr* (also called *Candida pseudotropicalis*), *Candida dubliniensis, Chlamydia pneumoniae, Chlamydia trachomatis, Clostridium acetobutylicum, Clostridium botulinum, Clostridium difficile, Clostridium perfringens, Coccidioides immitis, Corynebacterium diptheriae, Cryptococcus neoformans, Enterobacter*

30 *cloacae, Enterococcus faecalis, Enterococcus faecium, Escherichia coli, Haemophilus influenzae, Helicobacter pylori, Histoplasma capsulatum, Klebsiella pneumoniae, Legionella pneumophila, Listeria monocytogenes, Moraxella catarrhalis, Mycobacterium avium, Mycobacterium bovis, Mycobacterium leprae, Mycobacterium tuberculosis, Mycoplasma genitalium, Mycoplasma pneumoniae, Neisseria gonorrhoeae, Neisseria meningitidis, Nocardia asteroides, Pasteurella*

35 *haemolytica, Pasteurella multocida, Pneumocystis carinii, Proteus mirabilis, Proteus vulgaris, Pseudomonas aeruginosa, Pseudomonas putida, Pseudomonas syringae, Salmonella bongori, Salmonella cholerasuis, Salmonella enterica, Salmonella paratyphi, Salmonella typhi, Salmonella typhimurium, Shigella boydii, Shigella dysenteriae, Shigella flexneri, Shigella sonnei,*

Staphylococcus aureus, Staphylococcus epidermidis, Staphylococcus haemolyticus, Streptococcus pneumoniae, Streptococcus mutans, Streptococcus pyogenes, Treponema pallidum, Ureaplasma urealyticum, Vibrio cholerae, Vibrio parahaemolyticus, Vibrio vulnificans, Yersinia enterocolitica, Yersinia pestis or any species falling within the genera of any of the above species. In some

5   embodiments, the double stranded DNA may be introduced into an organism having the recBC and sbcA mutations or analogous mutations.

In other embodiments, a single stranded DNA to be inserted into the chromosome of the organism is introduced into an organism expressing the λ Beta protein or a protein with an analogous function. In some embodiments the single stranded DNA is introduced into an organism

10   expressing both the λ Beta and Gam proteins or proteins with analogous functions. In further embodiments, the single stranded DNA is introduced into an organism expressing the λ Beta, Gam and Exo proteins or proteins with analogous functions. The λ proteins or analogous proteins may be expressed constitutively or conditionally. In some embodiments, the organism may be Acinetobacter baumannii, Anaplasma marginale, Aspergillus fumigatus, Bacillus anthracis,

15   Bacteroides fragilis, Bordetella pertussis, Borrelia burgdorferi, Burkholderia cepacia, Burkholderia fungorum, Burkholderia mallei, Campylobacter jejuni, Candida albicans, Candida glabrata (also called Torulopsis glabrata), Candida tropicalis, Candida parapsilosis, Candida guilliermondii, Candida krusei, Candida kefyr (also called Candida pseudotropicalis), Candida dubliniensis, Chlamydia pneumoniae, Chlamydia trachomatis, Clostridium acetobutylicum,

20   Clostridium botulinum, Clostridium difficile, Clostridium perfringens, Coccidioides immitis, Corynebacterium diptheriae, Cryptococcus neoformans, Enterobacter cloacae, Enterococcus faecalis, Enterococcus faecium, Escherichia coli, Haemophilus influenzae, Helicobacter pylori, Histoplasma capsulatum, Klebsiella pneumoniae, Legionella pneumophila, Listeria monocytogenes, Moraxella catarrhalis, Mycobacterium avium, Mycobacterium bovis,

25   Mycobacterium leprae, Mycobacterium tuberculosis, Mycoplasma genitalium, Mycoplasma pneumoniae, Neisseria gonorrhoeae, Neisseria meningitidis, Nocardia asteroides, Pasteurella haemolytica, Pasteurella multocida, Pneumocystis carinii, Proteus mirabilis, Proteus vulgaris, Pseudomonas aeruginosa, Pseudomonas putida, Pseudomonas syringae, Salmonella bongori, Salmonella cholerasuis, Salmonella enterica, Salmonella paratyphi, Salmonella typhi, Salmonella

30   typhimurium, Shigella boydii, Shigella dysenteriae, Shigella flexneri, Shigella sonnei, Staphylococcus aureus, Staphylococcus epidermidis, Staphylococcus haemolyticus, Streptococcus pneumoniae, Streptococcus mutans, Streptococcus pyogenes, Treponema pallidum, Ureaplasma urealyticum, Vibrio cholerae, Vibrio parahaemolyticus, Vibrio vulnificans, Yersinia enterocolitica, Yersinia pestis or any species falling within the genera of any of the above species.

35   In some embodiments, the linear nucleic acid may be introduced into the chromosome of a first organism which has an enhanced frequency of homologous recombination and then transferred to a second organism which is less amenable to direct application of the present methods. For example, the linear nucleic acid may be introduced into the chromosome of E. coli and transferred

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into a second organism via conjugation or transduction. After introduction into the second organism, the nucleic acid is inserted into the chromosome of the second organism via homologous recombination, thereby effectively transferring the regulatory element from the chromosome of the first organism into the corresponding location in the chromosome of the second organism.

5   In other embodiments, the cells may be diploid cells, such as fungal cells. In some embodiments, one copy of the gene encoding the proliferation-required gene product may be disrupted, rendering it inactive. In further embodiments, one copy of the gene encoding the proliferation-required gene product may be disrupted and the other copy of the gene encoding the proliferation-required gene product may be placed under the control of a regulatable promoter.

10   Such strains may be generated by disrupting the first copy of the gene encoding the proliferation-required gene product by homologous recombination using a disruption cassette comprising a nucleotide sequence encoding an expressible dominant selectable marker flanked on each side by nucleic acids homologous to the target sequence to be disrupted. The second copy of the gene encoding the proliferation-required gene product may be placed under the control of a regulatable

15   promoter by homologous recombination using a promoter replacement cassette comprising a regulatable promoter flanked on each side by nucleic acids homologous to the natural promoter for the proliferation-required gene. The promoter replacement cassette may also include a nucleotide sequence encoding a selectable marker located 5' of the regulatable promoter but between the nucleic acids homologous to the natural promoter.

20   In other embodiments, overexpression may be achieved by operably linking a proliferation-required gene product described herein to a desired promoter in a vector. The vector may be a vector which replicates extrachromosomally or a vector which integrates into the chromosome. For example, if the vector is to be used in bacterial cells, the vector may be a pBR322 based vector or a bacteriophage based vector such as P1 or lambda. If the vector is to be used in *Saccharomyces*

25   *cerevisae*, it may be a vector based on the 2 micron circle or a vector incorporating a yeast chromosomal origin of replication. If the vector is to be used in mammalian cells, it may be a retroviral vector, SV40 based vector, a vector based on bovine papilloma virus, a vector based on adenovirus, or a vector based on adeno-associated virus. If the vector is to be used in *Candida albicans* it may be a vector comprising a promoter selected from the group consisting of the

30   CaPCK1, MET25, MAL2, PHO5, GAL1,10, STE2 or STE3 promoters. In some embodiments, the vectors described in the following publications may be used: CIp10, an efficient and convenient integrating vector for *Candida albicans*. Murad et al., Yeast 16(4):325-7 (2000); Transforming vector pCPW7, Kvaal et al., : Infect Immun 67(12):6652-62 (1999); Transforming vector pCWOP16, Kvaal et al., : Infect Immun 65(11):4668-75 (1997); double-ARS vector, pRM1, to be

35   used for direct cloning in Ca by complementation of the histidine auxotrophy of strain CA9, Pla et al., Gene 165(1):115-20 (1995); pMK16, that was developed for the transformation of *C. albicans* and carries an ADE2 gene marker and a *Candida* autonomously replicating sequence (CARS) element promoting autonomous replication (cited in Sanglard and Ficchter Yeast 8(12):1065-75

(1992); A plasmid vector (denoted pRC2312) was constructed, which replicates autonomously in *Escherichia coli, Saccharomyces cerevisiae* and *Candida albicans*. It contains LEU2, URA3 and an autonomously replicating sequence (ARS) from *C. albicans*, Cannon et al., Mol Gen Genet 235(2-3):453-7 (1992); Expression vector (CIp10-MAL2p) for use in *Candida albicans* has been

5   constructed in which a gene of interest can be placed under the control of the CaMAL2 maltase promoter and stably integrated at the CaRP10 locus (Backen et al., Yeast 16(12):1121-9 (2000)); (Volker, R. S., A. Sonneborn, C. E. Leuker, and J. F. Ernst. 1997. Efg1p, an essential regulator of morphogenesis of the human pathogen *Candida albicans*, is a member of a conserved class of bHLH proteins regulating morphogenetic processes in fungi. EMBO 16:1982-1991.); and a *C.*

10   *albicans* transformation vector containing the *C. albicans* URA3 gene, a Candida ARS sequence, and a portion of the *Saccharomyces cerevisiae* 2 microns circle containing the replication origin was constructed. Goshorn et al., Infect Immun 60(3):876-84 (1992). A variety of other vectors suitable for use in foregoing organisms or in any other organism in which the present invention is to be practiced are familiar to those skilled in the art.

15   Underexpression of a proliferation-required gene product described herein may be obtained in a variety of ways. For example, in one embodiment underexpression of the proliferation-required gene product may be achieved by providing an agent, such as an antisense nucleic acid comprising a nucleotide sequence selected from the group consisting of SEQ ID NOs.: 1-6213, an antisense nucleic acid comprising at least 10, 15, 20, 25, 30, 35, 40, 50, 75, 100, 150, 200, 300, 400,

20   or 500 consecutive nucleotides of a nucleotide sequence selected from the group consisting of SEQ ID NOs.: 1-6213, a nucleic acid complementary to a nucleic acid comprising a nucleotide sequence selected from the group consisting of SEQ ID NOs.: 6214-42397, a nucleic acid complementary to a nucleic acid comprising at least 10, 15, 20, 25, 30, 35, 40, 50, 75, 100, 150, 200, 300, 400, or 500 consecutive nucleotides of a nucleotide sequence selected from the group consisting of SEQ ID

25   NOs.: 6214-42397, a nucleic acid complementary to a nucleic acid which encodes a polypeptide comprising an amino acid sequence selected from the group consisting of SEQ ID NOs.: 42398-78581, a nucleic acid complementary to a nucleic acid which encodes at least 5, 10, 15, 20, 25, 30, 35, 40, 50, 75, 100, or 150 consecutive amino acids of a polypeptide sequence selected from the group consisting of SEQ ID NOs.: 42398-78581, a homologous antisense nucleic acid, an antisense

30   nucleic acid comprising at least 10, 15, 20, 25, 30, 35, 40, 50, 75, 100, 150, 200, 300, 400, or 500 consecutive nucleotides of a homologous nucleic acid, a nucleic acid complementary to a homologous coding nucleic acid, a nucleic acid complementary to at least 10, 15, 20, 25, 30, 35, 40, 50, 75, 100, 150, 200, 300, 400, or 500 consecutive nucleotides of a homologous coding nucleic acid, a nucleic acid complementary to a nucleic acid which encodes a homologous polypeptide, or a

35   nucleic acid complementary to a nucleic acid which encodes at least 5, 10, 15, 20, 25, 30, 35, 40, 50, 75, 100, or 150 consecutive amino acids of a homologous polypeptide, which reduces the level or activity of the gene product within the cell. In one embodiment, the agent may comprise an antisense nucleic acid comprising a nucleotide sequence selected from the group consisting of SEQ

ID NOs.: 1-6213 which is complementary to a nucleic acid encoding the proliferation-required gene product or complementary to a portion of a nucleic acid encoding the proliferation-required gene product.

In one example of antisense-inhibition-based underexpression, a nucleic acid which encodes the antisense nucleic acid may be operably linked to a regulatable promoter. When grown under appropriate conditions, such as media containing an inducer of transcription or an agent which alleviates repression of transcription, the antisense nucleic acid is expressed in the cell, thereby reducing the level or activity of the gene product within the cell. In some embodiments, the concentration of the inducer of transcription or the agent which alleviates repression of transcription may be varied to provide optimal results. Such methods have been described previously herein and in U.S. Patent Application Serial Number 09/815,242, U.S. Patent Application Serial Number 09/492,709, U.S. Patent Application Serial Number 09/711,164, or U.S. Patent Application Serial Number 09/741,669.

Alternatively, underexpression of a proliferation-required gene product described herein may be achieved by constructing strains in which the expression of the gene product is under the control of a constitutive or regulatable promoter using methods such as those described above with respect to methods in which the gene product is overexpressed. To provide cells which underexpress the gene product, the cells are grown under conditions in which the gene product is expressed at a level lower than that of a wild type cell. For example, the cells may be grown under conditions in which a repressor reduces the level of transcription from the regulatable promoter.

In other embodiments, underexpression may be achieved by operably linking the gene required for proliferation to a desired promoter in a vector as described above with respect to embodiments in which gene products required for proliferation are overexpressed. In some embodiments, the vector may be present in cells in which the chromosomal copy or copies of the gene has been disrupted.

Examples of gene products, which are encoded by genes that can be underexpressed using methods such as those described above with respect to methods in which the gene product is overexpressed include a gene product whose activity or level is inhibited by a nucleic acid comprising a nucleotide sequence selected from the group consisting of SEQ ID NOs.: 1-6213, a gene product encoded by a nucleic acid comprising a nucleotide sequence selected from the group consisting of SEQ ID NOs.: 6214-42397, a gene product comprising an amino acid sequence selected from the group consisting of SEQ ID NOs.: 42398-78581, a gene product whose activity or level is inhibited by a homologous antisense nucleic acid, a gene product encoded by a homologous coding nucleic acid, and a gene product comprising a homologous polypeptide.

One embodiment of the invention includes a method for identifying a gene product described herein on which a compound which inhibits the proliferation of an organism acts. The method employs a culture which comprises a mixture of strains of the organism. At least some of the strains in the culture overexpress a different gene product which is required for the proliferation

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of the organism. Preferably, each of the strains in the culture overexpresses a different gene product which is required for proliferation of the organism (i.e. all of the strains in the culture overexpress a gene product which is required for proliferation of the organism). For example, the gene product which is overexpressed in each strain may be a gene product whose activity or level is

5   inhibited by a nucleic acid comprising a nucleotide sequence selected from the group consisting of SEQ ID NOs.: 1-6213, a gene product encoded by a nucleic acid comprising a nucleotide sequence selected from the group consisting of SEQ ID NOs.: 6214-42397, a gene product comprising an amino acid sequence selected from the group consisting of SEQ ID NOs.: 42398-78581, a gene product whose activity or level is inhibited by a homologous antisense nucleic acid, a gene product

10   encoded by a homologous coding nucleic acid, and a gene product comprising a homologous polypeptide.

Strains that overexpress the proliferation-required gene product may be obtained using the methods described above. The culture may comprise any number of strains which overexpress a gene product required for proliferation. For example the culture may comprise at least two strains,

15   at least 10 strains, at least 20 strains, at least 30, strains, at least 50 strains, at least 100 strains, at least 300 strains or more than 300 strains which overexpress a gene product required for proliferation. In some embodiments, the culture may comprise strains which in aggregate overexpress all or most of the gene products required for proliferation of the organism.

The culture is contacted with a compound which inhibits proliferation of the organism. The

20   compound may be a candidate drug compound obtained from any source. For example, the compound may be a compound generated using combinatorial chemistry, a compound from a natural product library, or an impure or partially purified compound, such as a compound in a partially purified natural extract. The culture is contacted with a sufficient concentration of the compound to inhibit the proliferation of strains of the organism in the culture which do not

25   overexpress the gene product on which the compound acts, such that strains which overexpress said gene product on which the compound acts proliferate more rapidly in the culture than strains which do not overexpress said gene product on which said compound acts. Thus, after a sufficient period of time, the strain which overexpresses the gene product on which the compound acts will be more prevalent in the culture than strains which do not overexpress the gene product on which the

30   compound acts. In a preferred embodiment, the growth conditions and incubation period are selected so that only one strain, the strain overexpressing the target of the compound, is recovered from the culture. Thus, in one embodiment, a plurality of cultures containing a plurality of strains each of which overexpresses a different proliferation-required gene product may be grown in the presence of varying concentrations of the compound. In addition to varying the compound

35   concentrations, in embodiments where expression of the proliferation-required gene product is under the control of a regulatable promoter, the plurality of cultures may be grown at varying concentrations of an agent which regulates the level of expression from the promoter, such as an inducer or an agent which reduces the effect of a repressor on transcription from the promoter. It

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will be appreciated, that the cultures may be grown in liquid medium in the presence of the compound whose target is to be identified (and where appropriate in the presence of an agent which regulates the level of expression from the promoter) or alternatively, a liquid culture comprising the strains which overexpress the proliferation-required gene products may be grown in the absence of

5   the compound whose target is to be identified and then introduced onto a solid medium containing the compound (and, where appropriate, also containing an agent which regulates the level of expression from the promoter).

The identity of the overexpressed gene product which is the target of the compound may be determined using a variety of methods. For example, in some embodiments of the present

10   invention, the nucleic acids present in the culture or collection of strains which was contacted with the compound may be compared to the nucleic acids present in a control culture or collection of strains which was not contacted with the compound to identify nucleic acids which are overrepresented in the culture or collection of strains contacted with the test compound relative to the control culture or collection of strains. Alternatively, in some embodiments, the nucleic acids

15   present in a culture or collection of strains contacted with the test compound may be analyzed to identify those nucleic acids which are present without comparison to a control culture or collection of strains.

In some embodiments, the strains which proliferated more rapidly in the culture or collection of strains, i.e. strains having an enhanced ability to proliferate in the presence of a test

20   compound relative to other strains in the culture or collection of strains, are identified as follows. Amplification products which are correlated with each of the overexpressed genes and which are distinguishable from one another are obtained from a culture or collection grown in the presence of a test compound. The amplification products are distinguished from one another to determine whether a particular amplification product is overrepresented in the culture or collection of strains.

25   In some embodiments, the amplification products corresponding to each of the gene products have lengths which permit them to be distinguished from one another. In another embodiment, one or more of the amplification products have similar or identical lengths but are distinguishable from one another based on a detectable agent, such as a dye, attached thereto. In some embodiments, amplification products which are overrepresented are identified by comparing the amplification

30   products from the culture or collection of strains which was contacted with the test compound to the amplification products from a culture or collection of strains which was not contacted with the test compound. Alternatively, amplification products which are overrepresented may be identified by simply identifying the amplification products obtained from the culture or collection of strains contacted with the test compound (for example, only one or a few strains may have proliferated in

35   the presence of the test compound). The above methods for generating distinguishable amplification products may be used in conjunction with any of the methods for generating strains which overexpress gene products required for proliferation described herein in order to facilitate the

identification of strains which proliferate more rapidly or more slowly in the presence of a test compound.

For example, in some embodiments of the present invention, each of the native promoters of each of the genes encoding gene product required for proliferation are replaced by a single
5   desired replacement promoter. After growth of the culture or collection of strains containing the strains in which the promoters have been replaced in the presence of a test compound for a desired period of time, an amplification reaction is performed on nucleic acids obtained from the culture as follows.

The nucleic acids from the culture or collection of strains may be divided into at least two
10   aliquots if desired. In a preferred embodiment the nucleic acids from the culture or collection of strains are divided into four aliquots. A single primer complementary to a nucleotide sequence within the replacement promoter , within the proliferation required genes, or within nucleic acid sequences adjacent to the promoter or proliferation required genes is divided into at least two portions, one portion for each aliquot of nucleic acids. Each portion of the primer is labeled with a
15   distinct detectable dye, such as the 6FAM™, TET™, VIC™, HEX™, NED™, and PET™ dyes obtainable from Applied Biosystems (Foster City, CA). For example, the DS-31 or DS-33 dye sets available from Applied Biosystems (Foster City, CA) may be used to label the primers. Alternatively, the HEX™, NED, JOE, TMR and TET™ dyes available from Amersham Biosciences may be used. Thus, if the nucleic acids from the culture are not divided into aliquots, a
20   single primer labeled with a single dye may be used. If the nucleic acids from the culture are divided into aliquots, at least 2, at least 3, at least 4 or more than 4 primers labeled with distinguishable dyes may be used. Each of the portions of labeled primers are added to each of the aliquots of the nucleic acids from the culture or collection of strains such that each aliquot of nucleic acid receives a single labeled primer with a single detectable dye thereon. In some
25   embodiments, the primers are divided into 3 portions, 4 portions or more than 4 portions, with each portion having a dye which is distinguishable from the dyes on the other portions thereon.

Each of the aliquots of nucleic acids also receives a set of unlabeled primers, with each of the unlabeled primers being complementary to a nucleotide sequence within the promoter, within a nucleotide sequence which is unique to one of the genes encoding gene products required for
30   proliferation which were placed under the control of the replacement promoter, or within nucleotide sequences adjacent to the promoter or proliferation required genes. Each of the aliquots receives primers unique to 1/N proliferation required genes which were placed under the control of the replacement promoter, where N is the number of aliquots (i.e. if the culture or collection of strains consisted of 100 strains in which a gene required for proliferation was placed under the control of
35   the replacement promoter and was divided into four aliquots, then each of the four aliquots of nucleic acids from the culture or collection of strains would receive primers complementary to 25 of the genes). The unlabeled primers are selected so that each will yield an amplification product having a length distinguishable from the length of the amplification product produced with the other

unlabeled primers. Preferably, the amplification products are between about 100-about 400 nucleotides in length, but any lengths which may be distinguished from each other may be used. In addition, in some of the embodiments some of the amplification products may have identical or very similar lengths but be distinguishable from one another due to labeling with distinguishable dyes.

A nucleic acid amplification reaction is conducted on each of the nucleic acid aliquots. The amplification products are then separated by length to identify amplification products having increased representation in the culture or collection of strains (i.e. amplification products derived from cells which proliferated more rapidly in the culture or collection of strains). The amplification products are then correlated with the corresponding genes to determine which strains proliferated more rapidly in the culture or collection of strains. If desired, amplification products having increased representation in the culture may be identified by comparing the amplification products obtained from a culture or collection of strains which was contacted with the compound to amplification products obtained from a control culture or collection of strains which was not contacted with the compound. Alternatively, if desired, the amplification products which are obtained from a culture which was contacted with the compound may be directly identified without comparison to a control culture which was not contacted with the compound.

For example, in some embodiments, the amplification products from each of the nucleic acid aliquots are pooled and subjected to capillary electrophoresis. The amplification products are detected by detecting the fluorescent dyes attached thereto and their lengths are determined to identify those amplification products having increased or decreased representation in the culture or collection of strains. Figures 2A and 2B illustrate one embodiment of this method in which the absence of an amplification product from an amplification reaction performed on a culture comprising a plurality of strains underexpressing genes required for proliferation indicates that a test compound acts on the gene corresponding to the missing amplification product. It will be appreciated that the method may also be used to identify an amplification product which is overrepresented in an amplification reaction conducted on a culture or collection of strains overexpressing genes required for proliferation because the test compound acted on the corresponding gene.

Alternatively, in another embodiment, a first amplification reaction is performed on nucleic acids obtained from a culture or collection of strains which was contacted with the compound using a first primer complementary to a nucleotide sequence present upstream or downstream of all of the overexpressed genes (such as a primer complementary to a nucleotide sequence in a replacement promoter upstream of all of the overexpressed genes) and a set of primers complementary to a nucleotide sequence unique to each of the strains (such as a primer complementary to a nucleotide sequence within each of the proliferation-required genes). One of the two amplification primers for each of the proliferation required genes is labeled with a dye as described above. Preferably, the common primer complementary to a nucleotide sequence upstream or downstream of all of the

overexpressed genes is labeled with the dye. The primers used in the amplification reaction are designed so that the amplification product corresponding to each proliferation-required gene has a unique length or a dye which allows it to be distinguished from other amplification products of the same length. A second amplification reaction is conducted on a control culture or collection of

5   strains which was not contacted with the compound using the same primers as in the first amplification reaction. The amplification products from the first amplification reaction are compared to those from the second amplification reaction to identify one or more amplification products which are overrepresented in the culture or collection of strains. For example, the amplification products from the first amplification reaction may be run in a separate lane of a

10   polyacrylamide gel or a separate capillary than the amplification products from the second amplification reaction and the two lanes or capillaries are compared to one another. If desired, in the embodiment where the amplification products from the first amplification reaction are run in a different lane or capillary than the amplification products from the second amplification reaction, the same dye may be used to label the primers in the first and second amplification reactions.

15   Alternatively, if desired, different dyes may be used to label the primers in the first and second amplification reactions. If desired, in the embodiment where the amplification products from the first amplification reaction are run in a different lane or capillary than the amplification products from the second amplification reaction, the same dye may be used to label the primers in the first and second amplification reactions. Alternatively, if desired, different dyes may be used to label

20   the primers in the first and second amplification reactions.

Alternatively, in some embodiments, the primers in the second amplification reaction are labeled with a different dye which is distinguishable from the dye used in the first amplification reaction. In this embodiment, the amplification reactions may be pooled and run in the same lane on a polyacrylamide gel or in the same capillary and the products from each amplification reaction

25   are compared by comparing the amount of each dye present for each amplification product. Figures 3A and 3B illustrate one embodiment of this method in which the absence of an amplification product from the amplification reaction performed on a culture comprising a plurality of strains underexpressing genes required for proliferation which was contacted with the compound indicates that a test compound acts on the gene corresponding to the missing amplification product. It will be

30   appreciated that the method may also be used to identify an amplification product which is overrepresented in an amplification reaction conducted on a culture or collection of strains overexpressing genes required for proliferation because the test compound acted on the corresponding gene.

If desired, rather than dividing the culture into aliquots, individual amplification reactions

35   may be conducted on nucleic acids obtained from the culture or collection of strains. Each amplification reaction contains primers which will yield an amplification product specific for only one of the proliferation required genes. The resulting amplification products from each of the

individual amplification reactions are pooled and amplification products having increased representation in the culture are identified as described above.

In another embodiment, a culture or collection of strains in which gene products required for proliferation are overexpressed from regulatable promoters which replaced the native promoters
5   of the genes encoding these gene products is allowed to grow in the presence of a test compound for a desired number of generations. Preferably, the culture or collection of strains is allowed to grow in the presence of the test compound for at least 20 generations. Nucleic acids are isolated from the culture or collection of strains and an amplification reaction is performed using a primer which is complementary to a nucleotide sequence within the replacement promoter(s) or a nucleotide
10 sequence adjacent to the a 5' end thereof and primers which are complementary to a nucleotide sequence within the proliferation required genes or nucleotide sequences adjacent thereto. The resulting amplification product(s) is directly sequenced using a primer complementary to a nucleotide sequence within the replacement promoter.

In one embodiment of the present invention, the vector containing the nucleotide sequence
15 encoding the proliferation-required gene product is obtained from a strain which proliferated more rapidly in the culture using methods such as plasmid preparation techniques. Nucleic acid sequencing techniques are then employed to determine the nucleotide sequence of the gene which was overexpressed.

Alternatively, the identity of the overexpressed gene product which is the target of the
20 compound may be determined by performing a nucleic acid amplification reaction, such as a polymerase chain reaction (PCR), to identify the nucleotide sequence of the gene which was overexpressed. For example, aliquots of a nucleic acid preparation, such as a purified plasmid, from the strain which is recovered from the culture may each be contacted with pairs of PCR primers which would amplify a different proliferation-required gene to determine which pair of
25 primers yields an amplification product.

An alternative method for determining the identity of the gene product described herein which is the target of the compound involves obtaining a nucleic acid array, such as a DNA chip, which contains each of the proliferation-required genes which were overexpressed in the strains in the culture. Each proliferation-required gene occupies a known location in the array. A nucleic
30 acid preparation, such as a plasmid preparation, from the recovered strain is labeled with a detectable agent, such as radioactive or fluorescent moiety, and placed in contact with the nucleic acid array under conditions which permit the labeled nucleic acid to hybridize to complementary nucleic acids on the array. The location on the array to which the labeled nucleic acids hybridize is determined to identify the gene which was overexpressed in the recovered strain. If desired the
35 hybridized nucleic acids from a culture which was contacted with the compound may be compared to the hybridized nucleic acids from a control culture which was not contacted with the compound. Alternatively, the hybridized nucleic acids from a culture which was contacted with the compound may be directly identified without comparison to nucleic acids from a control culture.

In some instances, more than one strain may proliferate more rapidly in the presence of the compound. This may result from a variety of causes. For example, the concentration of the compound may not have been high enough to restrict proliferation only to cells which overexpress one gene product (i.e. the target gene product). While strains which overexpress the target gene product will be the most prevalent strain in the culture, other strains may also have proliferated. In such instances, the identity of the gene product in the strain which is most prevalent in the culture may be identified by quantitating the levels of each of the genes encoding proliferation-required proteins in the culture. This may be accomplished by quantitative PCR, DNA sequencing, hybridization, or array technology as described above.

In other instances, multiple strains will exhibit more rapid proliferation in the culture as a result of a common functional attribute. For example, the strains which proliferate more rapidly may each overexpress a gene product with a common enzymatic activity, such as serine protease activity for example. Alternatively, the strains which proliferate more rapidly may each overexpress a gene product with a common functional domain, such as a cAMP binding domain. In such instances, the common attribute of the strains which proliferate more rapidly may provide information as to the mode of action of the compound or the biochemical activity of the target of the compound. For example, if all of the overexpressed genes in the strains which proliferated more rapidly are serine proteases, the compound acts by inhibiting serine protease activity and the target protein is a serine protease. If desired, the compound may be derivatized and the efficacy of the derivatized compound against each of the strains which proliferated more rapidly may be assessed as described herein in order to identify derivatives which are capable of interacting with a wide range of targets sharing a common activity or binding site (i.e. derivatives which have a greater ability to inhibit the proliferation of all the strains than the original compound) or to identify derivatives having greater specificity for a desired target (i.e. derivatives which have a greater specificity for one of the strains than the original compound). For example, it is possible that a nonessential gene product expressed in the cell might also bind to the initial test compound in addition to the gene product required for proliferation. In such an instance, it is desirable to obtain a derivative of the initial test compound which is specific for the gene product required for proliferation. In addition, it is possible that two gene products required for proliferation might bind to the initial test compound but specificity for one of the gene products is desired.

Rather than employing a single culture which contains multiple strains each of which overexpresses a proliferation-required gene product described herein, the methods of the present invention may be performed using an array of individual strains (i.e. a collection of strains) each of which overexpresses a different proliferation-required gene product. For example, individual strains each overexpressing a different proliferation-required gene product may be grown in different wells of a multiwell plate. Each well is contacted with the compound (and, where appropriate an agent which regulates the level of expression from the promoter). The level of proliferation of the strains in each of the wells is determined to identify a strain which proliferated

more rapidly. The identity of the overexpressed gene product in the strain that proliferated more rapidly is determined as described above.

In another embodiment, individual strains each overexpressing a different proliferation-required gene product (i.e. a collection of strains) are grown at different locations on a solid
5 medium, such as an agar plate. The medium contains the compound and where appropriate an agent which regulates the level of expression from the promoter). The level of proliferation of each of the strains is determined to identify a strain which proliferated more rapidly. The identity of the overexpressed gene product in the strain that proliferated more rapidly is determined as described above.

10 The above methods may be used to prioritize compound development or to determine whether the compound has been previously identified or whether the target of the compound is the target of a previously identified drug. In particular, if the product is a natural product, it is advantageous to determine whether it has been previously identified prior to investing significant effort in developing it. Thus, in some embodiments of the present invention, the target of a partially
15 purified or purified natural product or a compound produced by combinatorial chemistry is identified using the methods described above and compared to the targets of known drugs. If the target is identical to that of a known drug, further development of the compound is halted.

Alternatively, an array of strains each of which overexpresses a different gene product described herein (i.e. a collection of strains) is grown on solid medium containing a compound to be
20 evaluated. The location of each strain in the array and the gene product overexpressed by that strain is known. The pattern of colonies which grow in the presence of the compound is evaluated and compared to the pattern of colonies which grow in the presence of previously identified drugs. If the pattern of colonies which grow in the presence of the compound being evaluated is the same as the pattern of colonies which grow in the presence of a previously identified drug, further
25 development of the compound is halted.

Additionally in some embodiments, the sequence of the gene product in a strain which proliferated more rapidly in the assays described above is compared to the sequence of gene products from heterologous organisms to determine the likely spectrum of species whose growth would be inhibited by the compound. If the gene product has a high degree of homology to gene
30 products from heterologous species, it is likely that the compound would also inhibit the growth of these heterologous species. Homology may be determined using any of a variety of methods familiar to those skilled in the art. For example, homology may be determined using a computer program such as BLASTP or FASTA. The ability of the compound to inhibit the growth of the heterologous species may then be confirmed by comparing the growth of cells of the heterologous
35 species in the presence and absence of the compound.

Current methods for identifying the target of compounds which inhibit cellular proliferation are laborious and time consuming. The above methods may be employed to allow the targets of a large number of compounds to be rapidly identified. In such methods, the methods described above

are simultaneously performed for each of a large number of compounds. For example, the compounds may be members of a library of compounds generated using combinatorial chemistry or members of a natural product library. In such methods, a plurality of cultures each comprising a plurality of strains each of which overexpresses a different gene product required for proliferation

5   or a plurality of collections of individual strains each of which overexpresses a different gene product required for proliferation is obtained. Each culture or collection of strains is contacted with a different compound in the library and the target of the compound is identified as described above.

       In another embodiment, the gene product described herein on which a compound which inhibits the proliferation of an organism acts is identified using a culture which comprises a mixture

10   of strains of the organism including strains which underexpress a different gene product which is required for proliferation of the organism (i.e. at least some of the strains in the culture underexpress a gene product which is required for proliferation of the organism). Preferably, each of the strains in the culture underexpress a different a gene product which is required for the proliferation of the organism (i.e. all of the strains in the culture underexpress a gene product which

15   is required for the proliferation of the organism). In some embodiments, the culture comprises at least one strain which underexpresses a gene product selected from the group consisting of a gene product whose activity or level is inhibited by a nucleic acid comprising a nucleotide sequence selected from the group consisting of SEQ ID NOs.: 1-6213, a gene product encoded by a nucleic acid comprising a nucleotide sequence selected from the group consisting of SEQ ID NOs.: 6214-

20   42397, a gene product comprising an amino acid sequence selected from the group consisting of SEQ ID NOs.: 42398-78581, a gene product whose activity or level is inhibited by a homologous antisense nucleic acid, a gene product encoded by a homologous coding nucleic acid, and a gene product comprising a homologous polypeptide.

       Strains underexpressing the proliferation-required gene products described herein may be

25   obtained using the methods described above. The culture may comprise any number of strains. For example the culture may comprise at least two strains, at least 10 strains, at least 20 strains, at least 30, strains, at least 50 strains, at least 100 strains, at least 300 strains or more than 300 strains which underexpress a gene product required for proliferation. In some embodiments, the strains in the culture in aggregate may underexpress all or most of the gene products required for proliferation of

30   the organism.

       The culture is contacted with a compound which inhibits proliferation of the organism. The compound may be a candidate drug compound obtained from any source. For example, the compound may be a compound generated using combinatorial chemistry, a compound from a natural product library, or an impure or partially purified compound, such as a compound in a

35   partially purified natural extract. The culture is contacted with a sufficient concentration of the compound to inhibit the proliferation of strains of the organism in the culture which underexpress the gene product on which the compound acts, such that strains which do not underexpress the gene product on which the compound acts proliferate more rapidly in the culture than strains which do

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underexpress said gene product on which said compound acts. Thus, after a sufficient period of
time, the strain which underexpresses the gene product on which the compound acts will be less
prevalent in the culture than strains which do not underexpress the gene product on which the
compound acts. In one embodiment, the growth conditions and incubation period are selected so
that only one strain, the strain underexpressing the target of the compound, proliferates at a reduced
rate in the culture. In another embodiment, the growth conditions may be selected so that the strain
underexpressing the target of the compound is not recovered from the culture. Thus, in one
embodiment, a plurality of cultures containing a plurality of strains each of which underexpresses a
different proliferation-required gene product may be grown in the presence of varying
concentrations of the compound. In addition to varying the compound concentrations, in
embodiments where expression of the proliferation-required gene product is under the control of a
regulatable promoter, the plurality of cultures may be grown at varying concentrations of an agent
which regulates the level of expression from the promoter, such as an inducer or an agent which
reduces the effect of a repressor on transcription from the promoter. It will be appreciated, that the
cultures may be grown in liquid medium in the presence of the compound whose target is to be
identified (and where appropriate in the presence of an agent which regulates the level of expression
from the promoter) or alternatively, a liquid culture comprising the strains which underexpress the
proliferation-required gene products may be grown in the absence of the compound whose target is
to be identified and then introduced onto a solid medium containing the compound (and, where
appropriate, also containing an agent which regulates the level of expression from the promoter).

The identity of the underexpressed gene product which is the target of the compound may
be determined using a variety of methods. For example, in some embodiments of the present
invention, the nucleic acids present in the culture or collection of strains which was contacted with
the compound may be compared to the nucleic acids present in a control culture or collection of
strains which was not contacted with the compound to identify nucleic acids which are
underrepresented in the culture or collection of strains contacted with the test compound relative to
the control culture or strains. Alternatively, in some embodiments, the nucleic acids present in a
culture or collection of strains contacted with the test compound may be analyzed to identify those
nucleic acids which are missing or present at reduced levels without comparison to a control culture
or collection of strains.

In some embodiments of the present invention, the strains which proliferated more slowly
in the culture or collection of strains, i.e. strains having an decreased ability to proliferate in the
presence of a test compound or which do not proliferate in the presence of a test compound, are
identified as follows. Amplification products which are correlated with each of the underexpressed
genes and which are distinguishable from one another are obtained from a culture or collection
grown in the presence of a test compound. The amplification products are distinguished from one
another to determine whether a particular amplification product is underrepresented in the culture or
collection of strains. In some embodiments, the amplification products corresponding to each of the

gene products have lengths which permit them to be distinguished from one another. In another embodiment, one or more of the amplification products have similar or identical lengths but are distinguishable from one another based on a detectable agent, such as a dye, attached thereto. In some embodiments, amplification products which are underrepresented are identified by comparing

5   the amplification products from the culture or collection of strains which was contacted with the test compound to the amplification products from a culture or collection of strains which was not contacted with the test compound. Alternatively, amplification products which are underrepresented in the culture or collection of strains may be identified simply by determining which amplification products are missing or present at reduced levels in the culture or collection of

10   strains. The above methods for generating distinguishable amplification products may be used in conjunction with any of the methods for generating strains which underexpress gene products required for proliferation described herein in order to facilitate the identification of strains which proliferate more slowly in the presence of a test compound.

For example, in some embodiments of the present invention, each of the native promoters of each

15   of the genes encoding gene product required for proliferation are replaced by a single desired replacement promoter. After growth of the culture or collection of strains containing the strains in which the promoters have been replaced in the presence of a test compound for a desired period of time, an amplification reaction is performed on nucleic acids obtained from the culture as follows.

The nucleic acids from the culture or collection of strains are divided into at least two

20   aliquots. In a preferred embodiment the nucleic acids from the culture or collection of strains are divided into four aliquots. A single primer complementary to a nucleotide sequence within the replacement promoter , within the proliferation required genes, or within nucleic acid sequences adjacent to the promoter or proliferation required genes is divided into four groups Each group is labeled with a distinct detectable dye, such as the 6FAM™, TET™, VIC™, HEX™, NED™, and

25   PET™ dyes obtainable from Applied Biosystems (Foster City, CA). For example, the DS-31 or DS-33 dye sets available from Applied Biosystems (Foster City, CA) may be used to label the primers. Each of the groups of labeled primers are added to each of the aliquots of the nucleic acids from the culture or collection of strains such that each aliquot of nucleic acid receives a single labeled primer with a single detectable dye thereon.

30   Each of the aliquots of nucleic acids also receives a set of unlabeled primers, with each of the unlabeled primers being complementary to a nucleotide sequence within the promoter, within a nucleotide sequence which is unique to one of the genes encoding gene products required for proliferation which were placed under the control of the replacement promoter, or within nucleotide sequences adjacent to the promoter or proliferation required genes. Each of the aliquots receives

35   primers unique to 1/N proliferation required genes which were placed under the control of the replacement promoter, where N is the number of aliquots (i.e. if the culture or collection of strains consisted of 100 strains in which a gene required for proliferation was placed under the control of the replacement promoter and was divided into four aliquots, then each of the four aliquots of

nucleic acids from the culture or collection of strains would receive primers complementary to 25 of the genes). The unlabeled primers are selected so that each will yield an amplification product having a length distinguishable from the length of the amplification product produced with the other unlabeled primers. Preferably, the amplification products are between about 100-about 400

5   nucleotides in length, but any lengths which may be distinguished from each other may be used. In addition, in some of the embodiments some of the amplification products may have identical or very similar lengths but be distinguishable from one another due to labeling with distinguishable dyes.

A nucleic acid amplification reaction is conducted on each of the nucleic acid aliquots. The

10   amplification products are then separated by length to identify amplification products decreased representation or which are absent in the culture or collection of strains. The amplification products are then correlated with the corresponding genes to determine which strains proliferated more slowly in the culture or collection of strains. If desired, amplification products having decreased representation in the culture may be identified by comparing the amplification products obtained

15   from a culture or collection of strains which was contacted with the compound to amplification products obtained from a control culture or collection of strains which was not contacted with the compound. Alternatively, if desired, the amplification products which are missing or present at reduced levels in a culture which was contacted with the compound may be directly identified without comparison to a control culture which was not contacted with the compound.

20   For example, in some embodiments, the amplification products from each of the nucleic acid aliquots are pooled and subjected to capillary electrophoresis. The amplification products are detected by detecting the fluorescent dyes attached thereto and their lengths are determined to identify those amplification products having decreased representation in the culture or collection of strains. Figures 2A and 2B illustrate one embodiment of this method in which the absence of an

25   amplification product from an amplification reaction performed on a culture comprising a plurality of strains underexpressing genes required for proliferation indicates that a test compound acts on the gene corresponding to the missing amplification product.

Alternatively, in another embodiment, a first amplification reaction is performed on nucleic acids obtained from a culture or collection of strains which was contacted with the compound using

30   a first primer complementary to a nucleotide sequence present upstream or downstream of all of the overexpressed genes (such as a primer complementary to a nucleotide sequence in a replacement promoter upstream of all of the overexpressed genes) and a set of primers complementary to a nucleotide sequence unique to each of the strains (such as a primer complementary to a nucleotide sequence within each of the proliferation-required genes). One of the two amplification primers for

35   each of the proliferation required genes is labeled with a dye as described above. Preferably, the common primer complementary to a nucleotide sequence upstream or downstream of all of the overexpressed genes is labeled with the dye. The primers used in the amplification reaction are designed so that the amplification product corresponding to each proliferation-required gene has a

unique length. A second amplification reaction is conducted on a control culture or collection of strains which was not contacted with the compound using the same primers as in the first amplification reaction. The amplification products from the first amplification reaction are compared to those from the second amplification reaction to identify one or more amplification

5   products which are underrepresented in the culture or collection of strains. For example, the amplification products from the first amplification reaction may be run in a separate lane of a polyacrylamide gel or a separate capillary than the amplification products from the second amplification reaction and the two lanes or capillaries are compared to one another.

Alternatively, in some embodiments, the primers in the second amplification reaction are

10   labeled with a different dye which is distinguishable from the dye used in the first amplification reaction. In this embodiment, the amplification reactions may be pooled and run in the same lane on a polyacrylamide gel or in the same capillary and the products from each amplification reaction are compared by comparing the amount of each dye present for each amplification product. Figures 3A and 3B illustrate one embodiment of this method in which the absence of an amplification

15   product from the amplification reaction performed on a culture comprising a plurality of strains underexpressing genes required for proliferation which was contacted with the compound indicates that a test compound acts on the gene corresponding to the missing amplification product.

If desired, rather than dividing the culture into aliquots, individual amplification reactions may be conducted on nucleic acids obtained from the culture or collection of strains. Each

20   amplification reaction contains primers which will yield an amplification product specific for only one of the proliferation required genes. The resulting amplification products from each of the individual amplification reactions are pooled and amplification products having decreased representation in the culture are identified as described above.

In an alternative embodiment, the representation of each strain in the culture may be

25   assessed by hybridizing detectably labeled nucleic acids encoding the proliferation-required gene products, or portions thereof, obtained from the culture to an array comprising nucleic acids encoding the gene products required for proliferation or portions thereof. Each nucleic acid encoding a gene product required for proliferation or portion thereof occupies a known location on the array. The signal from each location on the array is quantitated to identify those nucleic acids

30   encoding a proliferation-required gene product which are underrepresented in the culture. If desired the hybridized nucleic acids from a culture which was contacted with the compound may be compared to the hybridized nucleic acids from a control culture which was not contacted with the compound. Alternatively, the hybridized nucleic acids from a culture which was contacted with the compound may be directly analyzed without comparison to nucleic acids from a control culture.

35   In another alternative, each strain underexpressing a gene product required for proliferation may be constructed to contain a unique nucleic acid sequence (referred to herein as a "tag"). The tag may be included in the chromosome of each strain or in an extrachromosomal vector. For example, the tag could be included in a vector encoding an antisense nucleic acid complementary to

a gene encoding a gene product required for proliferation or a portion of such a gene or the tag may be included in the antisense nucleic acid itself. The representation of each strain in the culture may be assessed by performing an amplification reaction using primers complementary to each of the tags and quantitating the levels of the resulting amplification products to identify a tag which is

5   underrepresented or absent from the culture. Since each tag corresponds to one strain, the strain which is underrepresented or absent from the culture may be identified. If desired the tags present in a culture which was contacted with the compound may be compared to the tags present in a control culture which was not contacted with the compound. Alternatively, the tags present in a culture which was contacted with the compound may be analyzed without comparison to a control

10   culture.

It will be appreciated that, if desired, unique tags may also be used in embodiments in which gene products required for proliferation are overexpressed. In some aspects of such embodiments, the tags may be within or adjacent to the promoter which drives expression of the gene encoding the gene product. In such embodiments, the gene product which is overexpressed in

15   strains which proliferate more rapidly in the culture may be identified by detecting the presence or amount of the unique tag corresponding to that gene product in the culture.

In some instances, more than one strain may proliferate less rapidly in the presence of the compound. This may result from a variety of causes. For example, the concentration of the compound may not have been high enough to reduce the proliferation only in cells which

20   underexpress one gene product (i.e. the target gene product). While strains which underexpress the target gene product will be the least prevalent strain in the culture, other strains may also be underrepresented. In such instances, the identity of the gene product in the strain which is least prevalent in the culture (or not recovered from the culture) may be identified by quantitating the levels of each of the genes encoding proliferation-required proteins in the culture. This may be

25   accomplished by quantitative PCR, DNA sequencing, hybridization, or array technology as described above.

In other instances, multiple strains will exhibit less rapid proliferation in the culture as a result of a common functional attribute. For example, the strains which proliferate less rapidly (or the strains which are not recovered from the culture) may each underexpress a gene product with a

30   common enzymatic activity, such as serine protease activity for example. Alternatively, the strains which proliferate less rapidly (or the strains which are not recovered from the culture) may each underexpress a gene product with a common functional domain, such as a cAMP binding domain. In such instances, the common attribute of the strains which proliferate less rapidly (or the strains which are not recovered from the culture) may provide information as to the mode of action of the

35   compound or the biochemical activity of the target of the compound. For example, if all of the underexpressed genes in the strains which proliferated less rapidly are serine proteases, the compound acts by inhibiting serine protease activity and the target protein is a serine protease. If desired, the compound may be derivatized and the efficacy of the derivatized compound against

each of the strains which proliferated more rapidly may be assessed as described herein in order to identify derivatives which are capable of interacting with a wide range of targets sharing a common activity or binding site (i.e. derivatives which have a greater ability to inhibit the proliferation of all the strains than the original compound) or to identify derivatives having greater specificity for a

5   desired target (i.e. derivatives which have a greater specificity for one of the strains than the original compound).

Rather than employing a single culture which contains multiple strains each of which underexpresses a proliferation-required gene product described herein, the methods of the present invention may be performed using an array of individual strains (i.e. a collection of strains) each of

10   which underexpresses a different proliferation-required gene product. For example, individual strains each underexpressing a different proliferation-required gene product may be grown in different wells of a multiwell plate. Each well is contacted with the compound (and, where appropriate an agent which regulates the level of expression from the promoter). The level of proliferation of the strains in each of the wells is determined to identify a strain which proliferated

15   less rapidly or which did not proliferate at all. The identity of the underexpressed gene product in the strain that proliferated less rapidly or which did not proliferate at all is determined as described · above.

In another embodiment, individual strains each underexpressing a different proliferation-required gene product (i.e. a collection of strains) are grown at different locations on a solid

20   medium, such as an agar plate. The medium contains the compound and, where appropriate, an agent which regulates the level of expression from the promoter. The level of proliferation of each of the strains is determined to identify a strain which proliferated less rapidly (or a strain which is not recovered from the culture). The identity of the underexpressed gene product in the strain that proliferated less rapidly (or the strain which is not recovered from the culture) is determined as

25   described above.

The above methods may be used to prioritize compound development or to determine whether the compound has been previously identified or whether the target of the compound is the target of a previously identified drug. In particular, if the product is a natural product is advantageous to determine whether it has been previously identified prior to investing significant

30   effort in developing it. Thus, in some embodiments of the present invention, the target of a partially purified or purified natural product or a compound produced by combinatorial chemistry is identified using the methods described above and compared to the targets of known drugs. If the target is identical to that of a known drug, further development of the compound is halted.

Alternatively, an array of strains each of which underexpresses a different gene product

35   described herein (i.e. a collection of strains) is grown on solid medium containing a compound to be evaluated. The location of each strain in the array and the gene product underexpressed by that strain is known. The pattern of colonies which grow less rapidly or fail to grow in the presence of the compound is evaluated and compared to the pattern of colonies which grow less rapidly or fail

to grow in the presence of previously identified drugs. If the pattern of colonies which grow less rapidly or fail to grow in the presence of the compound being evaluated is the same as the pattern of colonies which grow less rapidly or fail to grow in the presence of a previously identified drug, further development of the compound is halted.

5   Additionally, the nucleotide sequence of the gene product described herein in a strain which proliferated less rapidly (or a strain which was not recovered from the culture) in the assays described above is compared to the nucleotide sequence of gene products from heterologous organisms to determine the likely spectrum of species whose growth would be inhibited by the compound. If the gene product has a high degree of homology to gene products from heterologous
10   species, it is likely that the compound would also inhibit the growth of these heterologous species. Homology may be determined using any of a variety of methods familiar to those skilled in the art. For example, homology may be determined using a computer program such as BLASTP or FASTA. The ability of the compound to inhibit the growth of the heterologous species may then be confirmed by comparing the growth of cells of the heterologous species in the presence and absence
15   of the compound.

        In other embodiments, the present invention uses collections or cultures of strains comprising both strains which overexpress gene products described herein required for cellular proliferation and strains which underexpress the same gene products required for cellular proliferation. The gene product which is overexpressed or underexpressed in each strain may be a
20   gene product whose activity or level is inhibited by a nucleic acid comprising a nucleotide sequence selected from the group consisting of SEQ ID NOs.: 1-6213, a gene product encoded by a nucleic acid comprising a nucleotide sequence selected from the group consisting of SEQ ID NOs.: 6214-42397, a gene product comprising an amino acid sequence selected from the group consisting of SEQ ID NOs.: 42398-78581, a gene product whose activity or level is inhibited by a homologous
25   antisense nucleic acid, a gene product encoded by a homologous coding nucleic acid, and a gene product comprising a homologous polypeptide.

        The culture or collection of strains is contacted with a compound and the nucleic acids present in the culture or collection of strains are analyzed. Preferably, nucleic acids derived from overexpressing strains can be distinguished from those derived from underexpressing strains. For
30   example, the overexpressing strains may be obtained using promoter replacement as described above while the underexpressing strains may be obtained by expressing antisense nucleic acids. Accordingly, in one embodiment, amplification primers may be designed which will uniquely amplify nucleic acids from the overexpressing strains or the underexpressing strains. If a compound acts on a gene product which was overexpressed and underexpressed in the culture, then
35   the amplification product obtained from the strain in the culture or collection which overexpressed gene product will be overrepresented in the culture or collection while the amplification product obtained from the strain which underexpressed the gene product will be underrepresented in the culture or collection. If desired, nucleic acids from a culture or collection which was contacted with

the compound may be compared to nucleic acids from a control culture or collection which was not contacted with the compound. Alternatively, nucleic acids from a culture or collection which was contacted with the compound may be directly analyzed without comparison to a control culture or collection.

5   In some embodiments, strains are constructed in which a nucleic acid complementary to a gene encoding a gene product described herein required for proliferation or a portion thereof is operably linked to a regulatable promoter. For example, in some embodiments, the strains may transcribe an antisense nucleic acid selected from the group consisting of SEQ ID NOs.: 1-6213 or fragments thereof which inhibit proliferation or reduce the activity or level of the gene product

10   encoded by the gene comprising a nucleotide sequence complementary to the antisense nucleic acid or homologous antisense nucleic acids or fragments thereof. In other embodiments, the strains may transcribe an antisense nucleic acid which reduces the activity or level of a gene product encoded by SEQ ID NOs.: 6214-42397, the polypeptides of SEQ ID NOs.: 42398-78581, homologous coding nucleic acids or homologous polypeptides. A culture comprising a plurality of such strains

15   wherein each strain expresses an antisense nucleic acid against a different gene product required for proliferation is grown in the presence of varying levels of a compound which inhibits proliferation and in the presence of varying levels of an agent which regulates the level of transcription from the regulatable promoter. Nucleic acids samples are obtained from the culture, detectably labeled and hybridized to a solid support comprising nucleic acids containing the genes encoding the

20   proliferation-required gene products or a portion thereof. The level of hybridization is quantitated for each nucleic acid encoding each of the proliferation-required gene products to determine the rate at which each of the strains proliferated in the culture. If the antisense nucleic acid expressed by a strain in the culture is not complementary to all or a portion of the gene encoding the target of the compound (i.e. a nonspecific strain), then the hybridization intensity for that strain will not be

25   correlated with the concentration of the compound (See Figure 4), while if the antisense nucleic acid expressed by a strain in the culture is complementary to all or a portion of the gene encoding the target of the compound, the hybridization intensity for that strain will be intimately correlated with the concentration of the compound (See Figure 5). In this manner, the target of the compound may be identified. It will be appreciated that, as described above, rather than growing the strains in

30   a single culture, each strain may be grown in a different location on a solid medium or in a different well of a multiwell plate.

        The methods described above can be simultaneously performed for each of a large number of compounds. For example, the compounds may be members of a library of compounds generated using combinatorial chemistry or members of a natural product library. In such methods, a plurality

35   of cultures each comprising a plurality of strains each of which overexpresses or underexpresses a different gene product required for proliferation or a plurality of collections of individual strains each of which overexpresses or underexpresses a different gene product required for proliferation is

obtained. Each culture or collection of strains is contacted with a different compound in the library and the target of the compound is identified as described above.

In still another embodiment, the antisense nucleic acids of the present invention (including the antisense nucelic acids of SEQ ID NOs. 1-6213 fragments thereof or homologous antisense nucleic
5   acids or fragements thereof) that inhibit bacterial growth or proliferation can be used as antisense therapeutics for killing bacteria. The antisense sequences can be complementary to one of SEQ ID NOs.: 6214-42397 or fragments thereof, homologous coding nucleic acids or fragments thereof. Alternatively, antisense therapeutics can be complementary to operons in which proliferation-required genes reside (i.e. the antisense nucleic acid may hybridize to a nucleotide sequence of any gene in the
10   operon in which the proliferation-required genes reside). Further, antisense therapeutics can be complementary to a proliferation-required gene or portion thereof with or without adjacent noncoding sequences, an intragenic sequence (i.e. a sequence within a gene), an intergenic sequence (i.e. a sequence between genes), a sequence spanning at least a portion of two or more genes, a 5' noncoding region or a 3' noncoding region located upstream or downstream from the actual sequence that is
15   required for bacterial proliferation or an operon containing a proliferation-required gene.

In addition to therapeutic applications, the present invention encompasses the use of nucleic acids complementary to nucleic acids required for proliferation as diagnostic tools. For example, nucleic acid probes comprising nucleotide sequences complementary to proliferation-required sequences that are specific for particular species of cells or microorganisms can be used as probes to
20   identify particular microorganism species or cells in clinical specimens. This utility provides a rapid and dependable method by which to identify the causative agent or agents of a bacterial infection. This utility would provide clinicians the ability to accurately identify the species responsible for the infection and amdminister a compound effective against it. In an extension of this utility, antibodies generated against proteins translated from mRNA transcribed from proliferation-required sequences
25   can also be used to screen for specific cells or microorganisms that produce such proteins in a species-specific manner.

Other embodiments of the present invention include methods of identifying compounds which inhibit the activity of gene products required for cellular proliferation using rational drug design. As discussed in more detail below, in such methods, the structure of the gene product is determined using
30   techniques such as x-ray crystallography or computer modeling. Compounds are screened to identify those which have a structure which would allow them to interact with the gene product or a portion thereof to inhibit its activity. The compounds may be obtained using any of a variety of methods familiar to those skilled in the art, including combinatorial chemistry. In some embodiments, the compounds may be obtained from a natural product library. In some embodiments, compounds having
35   a structure which allows them to interact with the active site of a gene product, such as the active site of an enzyme, or with a portion of the gene product which interacts with another biomolecule to form a complex are identified. If desired, lead compounds may be identified and further optimized to provide compounds which are highly effective against the gene product.

The following examples teach the genes of the present invention and a subset of uses for the genes identified as required for proliferation. These examples are illustrative only and are not intended to limit the scope of the present invention.

EXAMPLES

5   The following examples are directed to the identification and exploitation of genes required for proliferation. Methods of gene identification are discussed as well as a variety of methods to utilize the identified sequences. It will be appreciated that any of the antisense nucleic acids, proliferartion-required genes or proliferation-required gene products described herein, or portions thereof, may be used in the procedures described below, including the antisense nucleic acids of SEQ ID NOs.: 1-6213,

10   the nucleic acids of SEQ ID NOS.: 6214-42397, or the polypeptides of SEQ ID NOs.: 42398-78581. Likewise, homologous antisense nucleic acids, homologous coding nucleic acids, homologous polypeptides or portions of any of the above-mentioned nucleic acids or polypeptides, may be used in any of the procedures described below.

Genes Identified as Required for Proliferation of *Escherichia coli, Staphylococcus aureus,*

15   *Enterococcus faecalis, Klebsiella pneumoniae, Pseudomonas aeruginosa* and *Salmonella typhimurium.*

Genomic fragments were operably linked to an inducible promoter in a vector and assayed for growth inhibition activity. Example 1 describes the examination of a library of genomic fragments cloned into vectors comprising inducible promoters. Upon induction with xylose or IPTG, the vectors

20   produced an RNA molecule corresponding to the subcloned genomic fragments. In those instances where the genomic fragments were in an antisense orientation with respect to the promoter, the transcript produced was complementary to at least a portion of an mRNA (messenger RNA) encoding a *Escherichia coli, Staphylococcus aureus, Enterococcus faecalis, Klebsiella pneumoniae, Pseudomonas aeruginosa* or *Salmonella typhimurium* gene product such that they interacted with

25   sense mRNA produced from various *Escherichia coli, Staphylococcus aureus, Enterococcus faecalis, Klebsiella pneumoniae, Pseudomonas aeruginosa* or *Salmonella typhimurium* genes and thereby decreased the translation efficiency or the level of the sense messenger RNA thus decreasing production of the protein encoded by these sense mRNA molecules. In cases where the sense mRNA encoded a protein required for proliferation, bacterial cells containing a vector from which transcription

30   from the promoter had been induced failed to grow or grew at a substantially reduced rate. Additionally, in cases where the transcript produced was complementary to at least a portion of a non-translated RNA and where that non-translated RNA was required for proliferation, bacterial cells containing a vector from which transcription from the promoter had been induced also failed to grow or grew at a substantially reduced rate. In contrast, cells grown under non-inducing conditions grow at a

35   normal rate.

The above method was used to identify genes required for cellular proliferation in *Escherichia coli, Staphylococcus aureus, Enterococcus faecalis, Klebsiella pneumoniae, Pseudomonas aeruginosa* and *Salmonella typhimurium.* Additionally, a number of genes required for cellular

proliferation in *Escherichia coli, Staphylococcus aureus, Enterococcus faecalis, Klebsiella pneumoniae, Pseudomonas aeruginosa* and *Salmonella typhimurium*, which have been described in the following U.S. Patent Applications: U.S. Patent Application Serial Number 09/492,709, filed January 27, 2000; U.S. Patent Application Serial Number 09/711,164, filed November 9, 2000;

5   U.S. Patent Application Serial Number 09/741,669, filed December 19, 2000 and U.S. Patent Application Serial Number 09/815,242 filed March 21, 2001, U.S. Provisional Patent Application Serial Number 60/342,923, filed October 25, 2001, have been previously identified using the above method.

EXAMPLE 1

10   Inhibition of Bacterial Proliferation after Induction of Antisense Expression

To identify genes required for proliferation of *E. coli*, random genomic fragments were cloned into the IPTG-inducible expression vector pLEX5BA (Krause et al., J. Mol. Biol. 274: 365 (1997) or a modified version of pLEX5BA, pLEX5BA-3' in which a synthetic linker containing a T7 terminator was ligated between the PstI and HindIII sites of pLEX5BA. In particular, to

15   construct pLEX5BA-3', the following oligonucleotides were annealed and inserted into the PstI and HindIII sites of pLEX5BA:

5'-GTCTAGCATAACCCCTTGGGGCCTCTAAACGGGTCCTTGAGGGGTTTTTTGA-3' (SEQ ID NO: 78584)
5'-AGCTTCAAAAAACCCCTCAAGGACCCGTTTAGAGGCCCCAAGGGGTTAT
20   GCTAGACTGCA-3' (SEQ ID NO: 78585)

Random fragments of *E. coli* genomic DNA were generated by DNAseI digestion or sonication, filled in with T4 polymerase, and cloned into the SmaI site of pLEX5BA or pLEX5BA-3'. Upon activation or induction, the promoter transcribed the random genomic fragments.

A number of vectors which allow the production of transcripts which have an extended

25   lifetime in *E. coli* as well as other Gram negative bacteria can also be utilized in conjunction with these antisense inhibition experiments. Such vectors are described in U.S. Provisional Patent Application Serial Number 60/343,512, filed December 21, 2001. Briefly, the stabilized antisense RNA may comprise an antisense RNA which was identified as inhibiting proliferation as described above which has been engineered to contain at least one stem loop flanking each end of the

30   antisense nucleic acid. In some embodiments, the at least one stem-loop structure formed at the 5' end of the stabilized antisense nucleic acid comprises a flush, double stranded 5' end. In some embodiments, one or more of the stem loops comprises a rho independent terminator. In additional embodiments, the stabilized antisense RNA lacks a ribosome binding site. In further embodiments, the stabilized RNA lacks sites which are cleaved by one or more RNAses, such as RNAse E or

35   RNAse III. In some embodiments, the stabilized antisense RNA may be transcribed in a cell which the activity of at least one enzyme involved in RNA degradation has been reduced. For example, the activity of an enzyme such as RNase E, RNase II, RNase III, polynucleotide phosphorylase, and poly(A) polymerase, RNA helicase, enolase or an enzyme having similar functions may be reduced in the cell.

To study the effects of transcriptional induction in liquid medium, growth curves were carried out by back diluting cultures 1:200 into fresh media with or without 1 mM IPTG and measuring the OD_{450} every 30 minutes (min). To study the effects of transcriptional induction on solid medium, 10^2, 10^3, 10^4, 10^5, 10^6, 10^7 and 10^8 fold dilutions of overnight cultures were prepared. Aliquots of from 0.5

5   to 3 µl of these dilutions were spotted on selective agar plates with or without 1 mM IPTG. After overnight incubation, the plates were compared to assess the sensitivity of the clones to IPTG.

Of the numerous clones tested, some clones were identified as containing a sequence that inhibited *E. coli* growth after IPTG induction. Accordingly, the gene to which the inserted nucleic acid sequence corresponds, or a gene within the operon containing the inserted nucleic acid, is required for

10   proliferation in *E. coli*.

Nucleic acids involved in proliferation of *Staphylococcus aureus, Enterococcus faecalis, Klebsiella pneumoniae, Pseudomonas aeruginosa* and *Salmonella typhimurium* were identified as follows.   Randomly generated fragments of *Staphylococcus aureus, Enterococcus faecalis, Klebsiella pneumoniae, Pseudomonas aeruginosa* or *Salmonella typhimurium* genomic DNA were

15   transcribed from inducible promoters.

In the case of *Staphylococcus aureus*, a novel inducible promoter system, XylT5, comprising a modified T5 promoter fused to the *xylO* operater from the *xylA* promoter of *Staphylococcus aureus* was used. The promoter is described in U.S. Patent Application Serial Number 10/032,393, filed December 21, 2001. Transcription from this hybrid promoter is

20   inducible by xylose.

Randomly generated fragments of *Salmonella typhimurium* genomic DNA were transcribed from an IPTG inducible promoter in pLEX5BA (Krause et al., J. Mol. Biol. 274: 365 (1997) or a derivative thereof. Randomly generated fragements of *Klebsiella pneumoniae* genomic DNA were expressed from an IPTG inducible promoter in pLEX5BA-Kan. To construct

25   pLEX5BA-kan, pLEX5BA was digested to completion with *ClaI* in order to remove the *bla* gene. Then the plasmid was treated with a partial *NotI* digestion and blunted with T4 DNA polymerase. A 3.2 kbp fragment was then gel purified and ligated to a blunted 1.3 kbp kan gene from pKanπ. Kan resistant transformants were selected on Kan plates. Orientation of the kan gene was checked by *SmaI* digestion. A clone, which had the kan gene in the same orientation as the bla gene, was used

30   to identify genes required for proliferation of *Klebsiella pneumoniae*.   Randomly   generated fragments of *Pseudomonas aeruginosa* genomic DNA were trancribed from a two-component inducible promoter system. Integrated on the chromosome was the T7 RNA polymerase gene regulated by *lacUV5/ lacO* (Brunschwig, E. and Darzins, A. 1992. Gene 111:35-41. On a separate plasmid, a T7 gene 10 promoter, which is transcribed by T7 RNA polymerase, was fused with a

35   *lacO* operator followed by a multiple cloning site.

Should the genomic DNA downstream of the promoter contain, in an antisense orientation, at least a portion of an mRNA or a non-translated RNA encoding a gene product involved in proliferation, then induction of transcription from the promoter will result in detectable inhibition of proliferation.

5   In the case of *Staphylococcus aureus,* a shotgun library of *Staphylococcus aureus* genomic fragments was cloned into the vector pXylT5-P15a, which harbors the XylT5 inducible promoter. The vector was linearized at a unique *Bam*HI site immediately downstream of the XylT5 promoter/operator. The linearized vector was treated with shrimp alkaline phosphatase to prevent reclosure of the linearized ends. Genomic DNA isolated from *Staphylococcus aureus* strain RN450

10   was fully digested with the restriction enzyme *Sau*3A , or , alternatively, partially digested with DNase I and "blunt-ended" by incubating with T4 DNA polymerase. Random genomic fragments between 200 and 800 base pairs in length were selected by gel purification. The size-selected genomic fragments were added to the linearized and dephosphorylated vector at a molar ratio of 0.1 to 1, and ligated to form a shotgun library.

15   The ligated products were transformed into electrocompetent *E. coli* strain XL1-Blue MRF' (Stratagene) and plated on LB medium with supplemented with carbenicillin at 100 μg/ml. Resulting colonies numbering 5×10^5 or greater were scraped and combined, and were then subjected to plasmid purification.

The purified library was then transformed into electrocompetent *Staphylococcus aureus*
20   RN4220. Resulting transformants were plated on agar containing LB + 0.2% glucose (LBG medium) + chloramphenicol at 15 μg/ml (LBG+CM15 medium) in order to generate 100 to 150 platings at 500 colonies per plating. The colonies were subjected to robotic picking and arrayed into wells of 384 well culture dishes. Each well contained 100μl of LBG + CM15 liquid medium. Inoculated 384 well dishes were incubated 16 hours at 37°C, and each well was robotically gridded

25   onto solid LBG + CM15 medium with or without 2% xylose. Gridded plates were incubated 16 hours at 37°C, and then manually scored for arrayed colonies that were growth-compromised in the presence of xylose.

Arrayed colonies that were growth-sensitive on medium containing 2% xylose, yet were able to grow on similar medium lacking xylose, were subjected to further growth sensitivity
30   analysis as follows: Colonies from the plate lacking xylose were manually picked and inoculated into individual wells of a 96 well culture dish containing LBG + CM15, and were incubated for 16 hours at 37°C. These cultures were robotically diluted 1/100 into fresh medium and allowed to incubate for 4 hours at 37°C, after which they were subjected to serial dilutions in a 384 well array and then gridded onto media containing 2% xylose or media lacking xylose. After growth for 16

35   hours at 37°C, the arrays that resulted on the two media were compared to each other. Clones that grew similarly at all dilutions on both media were scored as a negative and were no longer considered. Clones that grew on xylose medium but failed to grow at the same serial dilution on the non-xylose plate were given a score based on the differential, i.e. should the clone grow at a

serial dilution of 10^4 or less on the xylose plate and grow at a serial dilution of 10^8 or less on the non-xylose plate, then the corresponding clone received a score of "4" representing the log difference in growth observed.

For *Salmonella typhimurium* and *Klebsiella pneumoniae* growth curves were carried out by back diluting cultures 1:200 into fresh media containing 1 mM IPTG or media lacking IPTG and measuring the OD_{450} every 30 minutes (min). To study the effects of transcriptional induction on solid medium, 10^2, 10^3, 10^4, 10^5, 10^6, 10^7 and 10^8 fold dilutions of overnight cultures were prepared. Aliquots of from 0.5 to 3 µl of these dilutions were spotted on selective agar plates with or without 1 mM IPTG. After overnight incubation, the plates were compared to assess the sensitivity of the clones to IPTG.

Nucleic acids involved in proliferation of *Pseudomonas aeruginosa* were identified as follows. Randomly generated fragments of *Pseudomonas aeruginosa* genomic DNA were transcribed from a two-component inducible promoter system. Integrated on the chromosome was the T7 RNA polymerase gene regulated by *lac*UV5/ *lac*O (Brunschwig, E. and Darzins, A. 1992. Gene 111:35-41). On an expression plasmid there was a T7 gene 10 promoter, which is transcribed by T7 RNA polymerase, fused with a *lac*O operator followed by a multiple cloning site. Transcription from this hybrid promoter is inducible by IPTG. Should the genomic DNA downstream of the promoter contain, in an antisense orientation, at least a portion of an mRNA encoding a gene product involved in proliferation, then induction of expression from the promoter will result in detectable inhibition of proliferation.

A shotgun library of *Pseudomonas aeruginosa* genomic fragments was cloned into the vectors pEP5, pEP5S, or other similarly constructed vectors which harbor the T7*lac*O inducible promoter. The vector was linearized at a unique *Sma*I site immediately downstream of the T7*lac*O promoter/operator. The linearized vector was treated with shrimp alkaline phosphatase to prevent reclosure of the linearized ends. Genomic DNA isolated from *Pseudomonas aeruginosa* strain PAO1 was partially digested with DNase I and "blunt-ended" by incubating with T4 DNA polymerase. Random genomic fragments between 200 and 800 base pairs in length were selected by gel purification. The size-selected genomic fragments were added to the linearized and dephosphorylated vector at a molar ratio of 2 to 1, and ligated to form a shotgun library.

The ligated products were transformed into electrocompetent *E. coli* strain XL1-Blue MRF' (Stratagene) and plated on LB medium with carbenicillin at 100 µg/ml or Streptomycin 100 µg/ml. Resulting colonies numbering 5×10^5 or greater were scraped and combined, and were then subjected to plasmid purification.

The purified library was then transformed into electrocompetent *Pseudomonas aeruginosa* strain PAO1. Resulting transformants were plated on LB agar with carbenicillin at 100 µg/ml or Streptomycin 40 µg/ml in order to generate 100 to 150 platings at 500 colonies per plating. The colonies were subjected to robotic picking and arrayed into wells of 384 well culture dishes. Each well contained 100 µl of LB + CB 100 or Streptomycin 40 liquid medium. Inoculated 384 well

dishes were incubated 16 hours at room temperature, and each well was robotically gridded onto solid LB + CB100 or Streptomycin 40 medium with or without 1 mM IPTG. Gridded plates were incubated 16 hours at 37°C, and then manually scored for arrayed colonies that were growth-compromised in the presence of IPTG.

5   Arrayed colonies that were growth-sensitive on medium containing 1 mM IPTG, yet were able to grow on similar medium lacking IPTG, were subjected to further growth sensitivity analysis as follows: Colonies from the plate lacking IPTG were manually picked and inoculated into individual wells of a 96 well culture dish containing LB + CB100 or Streptomycin 40, and were incubated for 16 hours at 30°C. These cultures were robotically diluted 1/100 into fresh medium
10   and allowed to incubate for 4 hours at 37°C, after which they were subjected to serial dilutions in a 384 well array and then gridded onto media with and without 1 mM IPTG. After growth for 16 hours at 37°C, the arrays of serially diluted spots that resulted were compared between the two media. Clones that grew similarly at all dilutions on both media were scored as a negative and were no longer considered. Clones that grew on IPTG medium but failed to grow at the same serial
15   dilution on the non-IPTG plate were given a score based on the differential, i.e. should the clone grow at a serial dilution of 10^4 or less on the IPTG plate and grow at a serial dilution of 10^3 or less on the IPTG plate, then the corresponding clone received a score of "4" representing the log difference in growth observed.

Following the identification of those vectors that, upon induction, negatively impacted
20   *Pseudomonas aeruginosa* growth or proliferation, the inserts or nucleic acid fragments contained in those vectors were isolated for subsequent characterization. Vectors of interest were subjected to nucleic acid sequence determination.

Nucleic acids involved in proliferation of *E. faecalis* were identified as follows. Randomly generated fragments of genomic DNA were expressed from the vectors pEPEF3 or pEPEF14,
25   which contain the CP25 or P59 promoter, respectively, regulated by the xyl operator/repressor. These plasmids as well as other vectors useful for the expression of nucleic acids in *Enterococcus faecalis* and other Gram positive organisms are described in U.S. Patent Application Serial Number 10/032,393, filed December 21, 2001, the disclosure or which is incorporated herein by reference in its entirety. Should the genomic DNA downstream of the promoter contain, in an antisense
30   orientation, at least a portion of a mRNA encoding a gene product involved in proliferation, then induction of expression from the promoter will result in detectable inhibition of proliferation.

A shotgun library of *E. faecalis* genomic fragments was cloned into the vector pEPEF3 or pEPEF14, which harbor xylose inducible promoters. The vector was linearized at a unique *Sma*I site immediately downstream of the promoter/operator. The linearized vector was treated with
35   alkaline phosphatase to prevent reclosure of the linearized ends. Genomic DNA isolated from *E. faecalis* strain OG1RF was partially digested with DNase I and "blunt-ended" by incubating with T4 DNA polymerase. Random genomic fragments between 200 and 800 base pairs in length were

selected by gel purification. The size-selected genomic fragments were added to the linearized and dephosphorylated vector at a molar ratio of 2 to 1, and ligated to form a shotgun library.

The ligated products were transformed into electrocompetent *E. coli* strain TOP10 cells (Invitrogen) and plated on LB medium with erythromycin (Erm) at 150 μg/ml. Resulting colonies
5   numbering 5 x 10^5 or greater were scraped and combined, and were then subjected to plasmid purification.

The purified library was then transformed into electrocompetent *E. faecalis* strain OG1RF. Resulting transformants were plated on Todd-Hewitt (TH) agar with erythromycin at 10 μg/ml in order to generate 100 to 150 platings at 500 colonies per plating. The colonies were subjected to
10   robotic picking and arrayed into wells of 384 well culture dishes. Each well contained 100 μl of THB + Erm 10 μg/ml. Inoculated 384 well dishes were incubated 16 hours at room temperature, and each well was robotically gridded onto solid TH agar ÷ Erm with or without 5% xylose. Gridded plates were incubated 16 hours at 37°C, and then manually scored for arrayed colonies that were growth-compromised in the presence of xylose.

15   Arrayed colonies that were growth-sensitive on medium containing 5% xylose, yet were able to grow on similar medium lacking xylose, were subjected to further growth sensitivity analysis. Colonies from the plate lacking xylose were manually picked and inoculated into individual wells of a 96 well culture dish containing THB + Erm 10, and were incubated for 16 hours at 30°C. These cultures were robotically diluted 1/100 into fresh medium and allowed to
20   incubate for 4 hours at 37°C, after which they were subjected to serial dilution on plates containing 5% xylose or plates lacking xylose. After growth for 16 hours at 37°C, the arrays of serially diluted spots that resulted were compared between the two media. Colonies that grew similarly on both media were scored as a negative and corresponding colonies were no longer considered. Colonies on xylose medium that failed to grow to the same serial dilution compared to those on the non-
25   xylose plate were given a score based on the differential. For example, colonies on xylose medium that only grow to a serial dilution of -4 while they were able to grow to -8 on the non-xylose plate, then the corresponding transformant colony received a score of "4" representing the log difference in growth observed.

Following the identification of those vectors that, upon induction, negatively impacted *E.*
30   *faecalis* growth or proliferation, the inserts or nucleic acid fragments contained in those expression vectors were isolated for subsequent characterization. The inserts in the vectors of interest were subjected to nucleotide sequence determination.

It will be appreciated that other restriction enzymes and other endonucleases or methodologies may be used to generate random genomic fragments. In addition, random genomic
35   fragments may be generated by mechanical shearing. Sonication and nebulization are two such techniques commonly used for mechanical shearing of DNA.

EXAMPLE 2

Nucleotide Sequence Determination of Identified Clones Transribing Nucleic Acid Fragments with
Detrimental Effects on *Escherichia coli, Staphylococcus aureus, Enterococcus faecalis, Klebsiella
pneumoniae, Pseudomonas aeruginosa* or *Salmonella typhimurium* Proliferation

5   Plasmids from clones that received a dilution plating score of "2" or greater were isolated to
obtain the genomic DNA insert responsible for growth inhibition as follows.

       The nucleotide sequences of the nucleic acid sequences which inhibited the growth of
Escherichia coli were determined using plasmid DNA isolated using QIAPREP (Qiagen, Valencia,
CA) and methods supplied by the manufacturer. The primers used for sequencing the inserts were 5' -

10   TGTTTATCAGACCGCTT - 3' (SEQ ID NO: 78586) and 5' - ACAATTTCACACAGCCTC - 3'
(SEQ ID NO: 78587). These sequences flank the polylinker in pLEX5BA.

       The nucleotide sequences of the nucleic acid sequences which inhibited the growth of
Staphylococcus aureus were determined as follows. *Staphylococcus aureus* were grown in standard
laboratory media (LB or TB with 15 ug/ml Chloramphenicol to select for the plasmid). Growth

15   was carried out at 37°C overnight in culture tubes or 2 ml deep well microtiter plates.

       Lysis of *Staphylococcus aureus* was performed as follows. Cultures (2-5 ml) were
centrifuged and the cell pellets resuspended in 1.5 mg/ml solution of lysostaphin (20 µl/ml of
original culture) followed by addition of 250 µl of resuspension buffer (Qiagen). Alternatively, cell
pellets were resuspended directly in 250 µl of resuspension buffer (Qiagen) to which 5-20 µl of a 1

20   mg/ml lysostaphin solution were added.

       DNA was isolated using Qiagen miniprep kits or Wizard (Qiagen) miniprep kits according
to the instructions provided by the manufacturer.

       The genomic DNA inserts were amplified from the purified plasmids by PCR as follows.

       1 µl of Qiagen purified plasmid was put into a total reaction volume of 25 µl Qiagen Hot

25   Start PCR mix. For *Staphylococcus aureus*, the following primers were used in the PCR reaction:
pXylT5F: CAGCAGTCTGAGTTATAAAATAG (SEQ ID NO: 78588)
LexL TGTTTATCAGACCGCTT (SEQ ID NO: 78589)

       Similar methods were conducted for *Salmonella typhimurium* and *Klebsiella pneumoniae.*
For *Salmonella typhimurium* and *Klebsiella pneumoniae* the following primers were used:

30   5' - TGTTTATCAGACCGCTT - 3' (SEQ ID NO: 78589) and
5'-ACAATTTCACACAGCCTC-3' (SEQ ID NO: 78587)
PCR was carried out in a PE GenAmp with the following cycle times:
Step 1. 95° C 15 min
Step 2. 94° C 45 sec

35   Step 3. 54° C 45 sec
Step 4. 72° C 1 minute
Step 5. Return to step 2, 29 times
Step 6. 72° C 10 minutes

Step 7. 4° C hold

The PCR products were cleaned using Qiagen Qiaquick PCR plates according to the manufacturer's instructions.

For *Pseudomonas aeruginosa,* plasmids from transformant colonies that received a dilution
5   plating score of "2" or greater were isolated to obtain the genomic DNA insert responsible for growth inhibition as follows. *Pseudomonas aeruginosa* were grown in standard laboratory media (LB with carbenicillin at 100 µg/ml or Streptomycin 40 µg/ml to select for the plasmid). Growth was carried out at 30°C overnight in 100 ul culture wells in microtiter plates. To amplify insert DNA 2 ul of culture were placed into 25 ul Qiagen Hot Start PCR mix. PCR reactions were in 96
10   well microtiter plates. For plasmid pEP5S the following primers were used in the PCR reaction:

T7L1+: GTCGGCGATATAGGCGCCAGCAACCG (SEQ ID NO: 78590)

pStrA3: ATAATCGAGCATGAGTATCATACG (SEQ ID NO: 78591)

PCR was carried out in a PE GenAmp with the following cycle times:

Step 1. 95° C 15 min
15   Step 2. 94° C 45 sec

Step 3. 54° C 45 sec

Step 4. 72° C 1 minute

Step 5. Return to step 2. 29 times

Step 6. 72° C 10 minutes
20   Step 7. 4° C hold

The PCR products were cleaned using Qiagen Qiaquick PCR plates according to the manufacturer's instructions.

The purified PCR products were then directly cycle sequenced with Qiagen Hot Start PCR mix. The following primers were used in the sequencing reaction:
25   T7/L2: ATGCGTCCGGCGTAGAGGAT (SEQ ID NO: 78592)

PCR was carried out in a PE GenAmp with the following cycle times:

Step 1. 94° C 15 min

Step 2. 96° C 10 sec

Step 3. 50° C 5 sec
30   Step 4. 60 C 4 min

Step 5. Return to step 2, 24 times

Step 6. 4° C hold

The PCR products were cleaned using Qiagen Qiaquick PCR plates according to the manufacturer's instructions.
35   For *E. faecalis,* plasmids from transformant colonies that received a dilution plating score of "2" or greater were isolated to obtain the genomic DNA insert responsible for growth inhibition as follows. *E. faecalis* were grown in THB 10 µg/ml Erm at 30°C overnight in 100 ul culture wells

in microtiter plates. To amplify insert DNA 2 ul of culture were placed into 25 μl Qiagen Hot Start

PCR mix. PCR reactions were in 96 well microtiter plates. The following primers were used in the

PCR reaction:

pXylT5: CAGCAGTCTGAGTTATAAAATAG (SEQ ID NO: 78588) and the

5   pEP/pAK1 primer.

PCR was carried out in a PE GenAmp with the following cycle times:

Step 1. 95° C 15 min

Step 2. 94° C 45 sec

Step 3. 54° C 45 sec

10   Step 4. 72° C 1 minute

Step 5. Return to step 2, 29 times

Step 6. 72° C 10 minutes

Step 7. 4° C hold

The PCR products were cleaned using Qiagen Qiaquick PCR plates according to the manufacturer's

15   instructions.

The purified PCR products were then directly cycle sequenced with Qiagen Hot Start PCR

mix. The following primers were used in the PCR reaction:

pXylT5: CAGCAGTCTGAGTTATAAAATAG (SEQ ID NO: 78588)

PCR was carried out in a PE GenAmp with the following cycle times:

20   Step 1. 94° C 15 min

Step 2. 96° C 10 sec

Step 3. 50° C 5 sec

Step 4. 60° C 4 min

Step 5. Return to step 2, 24 times

25   Step 6. 4° C hold

The PCR products were cleaned using Qiagen Qiaquick PCR plates according to the

manufacturer's instructions.

The amplified genomic DNA inserts from each of the above procedures were subjected to

automated sequencing. Sequence identification numbers (SEQ ID NOs) and clone names for the

30   identified inserts are listed in Table 1A and discussed below.

TABLE 1A

SeqID	Clone Name	SeqID	Clone Name	SeqID	Clone Name	SeqID	Clone Name	SeqID	Clone Name
1	E3M10000001B01	1243	P33-1.C22	2485	E1M10000260G02	3727	P1M10000105C04	4969	S1M10000025G06
2	E3M10000001A02	1244	X3S107-17	2486	E1M10000260F04	3728	P1M10000105D04	4970	S1M10000025H06
3	E3M10000001B02	1245	P35-7	2487	E1M10000260A05	3729	P1M10000105C05	4971	S1M10000025H07
4	E3M10000001C02	1246	X3S118-9	2488	E1M10000260C05	3730	P1M10000105B06	4972	S1M10000025A08
5	E3M10000001D02	1247	X3S163-1	2489	E1M10000260E05	3731	P1M10000105C08	4973	S1M10000025D08
6	E3M10000001E02	1248	X3S204-7	2490	E1M10000260C07	3732	P1M10000105H08	4974	S1M10000025F08
7	E3M10000001F02	1249	X3S177-4	2491	E1M10000260G07	3733	P1M10000105D09	4975	S1M10000025H08
8	E3M10000001G02	1250	P342-3	2492	E1M10000260B08	3734	P1M10000110E01	4976	S1M10000025A09
9	E3M10000001H02	1251	SC21.1	2493	E1M10000260D08	3735	P1M10000110F01	4977	S1M10000025B09
10	E3M10000001E03	1252	SC17.1	2494	E1M10000260E08	3736	P1M10000110G01	4978	S1M10000025C09
11	E3M10000001G03	1253	SC13.1	2495	E1M10000260E09	3737	P1M10000110B02	4979	S1M10000025D09
12	E3M10000001H03	1254	MC9.6	2496	E1M10000260C10	3738	P1M10000110B03	4980	S1M10000025E09
13	E3M10000001D04	1255	Z60-P16	2497	E1M10000260D10	3739	P1M10000110F03	4981	S1M10000025F09
14	E3M10000001E04	1256	Z86-I21	2498	E1M10000260E10	3740	P1M10000110G03	4982	S1M10000025A10
15	E3M10000001F04	1257	E1M10000109A02	2499	E1M10000260G10	3741	P1M10000110D04	4983	S1M10000025C10
16	E3M10000001G04	1258	E1M10000109A11	2500	E1M10000260H10	3742	P1M10000110F04	4984	S1M10000025D10
17	E3M10000001H04	1259	E1M10000101F05	2501	E1M10000260H11	3743	P1M10000110B05	4985	S1M10000025F10
18	E3M10000001B05	1260	E1M10000101D06	2502	E1M10000260B12	3744	P1M10000110E05	4986	S1M10000025G10
19	E3M10000001D05	1261	E1M10000101A07	2503	E1M10000260D12	3745	P1M10000110B07	4987	S1M10000025H10
20	E3M10000001G05	1262	E1M10000101H07	2504	E1M10000260G12	3746	P1M10000110B08	4988	S1M10000025C11
21	E3M10000001A06	1263	E1M10000101H09	2505	E1M10000261F01	3747	P1M10000110F08	4989	S1M10000025F11
22	E3M10000001F06	1264	E1M10000101C12	2506	E1M10000261B02	3748	P1M10000110A09	4990	S1M10000025B12
23	E3M10000001B08	1265	E1M10000103B04	2507	E1M10000261H02	3749	P1M10000110E09	4991	S1M10000025F12
24	E3M10000001E08	1266	E1M10000103D11	2508	E1M10000261G04	3750	P1M10000110F09	4992	S1M10000026C01
25	E3M10000001C09	1267	E1M10000110G01	2509	E1M10000261H05	3751	P1M10000100F01	4993	S1M10000026E01
26	E3M10000001D09	1268	E1M10000110H01	2510	E1M10000261G06	3752	P1M10000098A02	4994	S1M10000026F01
27	E3M10000001E09	1269	E1M10000110E09	2511	E1M10000261H06	3753	P1M10000098B02	4995	S1M10000026G01
28	E3M10000001B10	1270	E1M10000110A12	2512	E1M10000261D08	3754	P1M10000098A03	4996	S1M10000026H01
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30	E3M10000004G01	1272	E1M10000113F02	2514	E1M10000261C09	3756	P1M10000098E04	4998	S1M10000026B02
31	E3M10000004D02	1273	E1M10000113A11	2515	E1M10000261H09	3757	P1M10000098G04	4999	S1M10000026H02
32	E3M10000004C03	1274	E1M10000111C03	2516	E1M10000261E10	3758	P1M10000098A05	5000	S1M10000026B03
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36	E3M10000004F10	1278	E1M10000115G02	2520	E1M10000262F02	3762	P1M10000098C07	5004	S1M10000026A04
37	E3M10000004E11	1279	E1M10000115E03	2521	E1M10000262D03	3763	P1M10000098F07	5005	S1M10000026D04
38	E3M10000004H11	1280	E1M10000115G04	2522	E1M10000262G04	3764	P1M10000098A08	5006	S1M10000026F04
39	E3M10000005B01	1281	E1M10000115C06	2523	E1M10000262C05	3765	P1M10000098G08	5007	S1M10000026G04
40	E3M10000005C01	1282	E1M10000116B01	2524	E1M10000262A06	3766	P1M10000098H09	5008	S1M10000026H04
41	E3M10000005E01	1283	E1M10000106D02	2525	E1M10000262A07	3767	P1M10000098B11	5009	S1M10000026A05
42	E3M10000005E02	1284	E1M10000106G02	2526	E1M10000262E07	3768	P1M10000098C12	5010	S1M10000026B05
43	E3M10000005C03	1285	E1M10000106E04	2527	E1M10000262E08	3769	P1M10000099D01	5011	S1M10000026D05
44	E3M10000005D03	1286	E1M10000106F05	2528	E1M10000262B10	3770	P1M10000099G03	5012	S1M10000026F05
45	E3M10000005E03	1287	E1M10000106H05	2529	E1M10000262H10	3771	P1M10000099A09	5013	S1M10000026G05
46	E3M10000005C04	1288	E1M10000106H06	2530	F1M10000262G11	3772	P1M10000099A10	5014	S1M10000026H05
47	E3M10000005D04	1289	E1M10000106A08	2531	E1M10000262D12	3773	P1M10000099E10	5015	S1M10000026A06
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53	E3M10000005E08	1295	E1M10000123C09	2537	E1M10000263B07	3779	P1M10000106F04	5021	S1M10000026A07
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56	E3M10000006C01	1298	E1M10000123F11	2540	E1M10000263A11	3782	P1M10000107E02	5024	S1M10000026D07
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59	E3M10000006D03	1301	E1M10000107G02	2543	E1M10000263D12	3785	P1M10000107A04	5027	S1M10000026H07
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63	E3M10000006E11	1305	E1M10000107G08	2547	E1M10000264D03	3789	P1M10000107D10	5031	S1M10000026F08
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66	E3M10000007F01	1308	E1M10000117C12	2550	E1M10000264B04	3792	P1M10000108A02	5034	S1M10000026E09
67	E3M10000007G01	1309	E1M10000118C04	2551	E1M10000264C04	3793	P1M10000108B02	5035	S1M10000026G09
68	E3M10000007A02	1310	E1M10000118B05	2552	E1M10000264E04	3794	P1M10000108A03	5036	S1M10000026H09
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72	E3M10000007D03	1314	E1M10000119D03	2556	E1M10000264G09	3798	P1M10000108F05	5040	S1M10000026E10
73	E3M10000007H03	1315	E1M10000119A04	2557	E1M10000264D11	3799	P1M10000108F06	5041	S1M10000026F10
74	E3M10000007C04	1316	E1M10000131H01	2558	E1M10000264F11	3800	P1M10000108G06	5042	S1M10000026G10
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76	E3M10000007F06	1318	E1M10000131C06	2560	E1M10000264B12	3802	P1M10000109C03	5044	S1M10000026A11
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78	E3M10000008H02	1320	E1M10000131C07	2562	E1M10000265A02	3804	P1M10000109D04	5046	S1M10000026C11
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81	E3M10000008C08	1323	E1M10000135B02	2565	E1M10000265D04	3807	P1M10000109H09	5049	S1M10000026C12
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86	E3M10000009E02	1328	E1M10000133A06	2570	E1M10000265E09	3812	S4M10000001C01	5054	S1M10000027G01
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91	E3M10000009C07	1333	E1M10000144E03	2575	E1M10000265C11	3817	S4M10000019H06	5059	S1M10000027H02
92	E3M10000009C09	1334	E1M10000144F05	2576	E1M10000266D02	3818	S4M10000008H10	5060	S1M10000027D03
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94	E3M10000010H02	1336	E1M10000144G06	2578	E1M10000266F04	3820	S4M10000009C06	5062	S1M10000027G03
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98	E3M10000010G09	1340	E1M10000145E01	2582	E1M10000266F11	3824	S4M10000009F11	5066	S1M10000027H04
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101	E3M10000011B03	1343	E1M10000146E05	2585	E1M10000267A05	3827	S4M10000010H04	5069	S1M10000027D05
102	E3M10000011D03	1344	E1M10000124E02	2586	E1M10000267B05	3828	S4M10000010B05	5070	S1M10000027E05
103	E3M10000011C07	1345	E1M10000124G03	2587	E1M10000267A07	3829	S4M10000010D07	5071	S1M10000027F05
104	E3M10000011A09	1346	E1M10000124G04	2588	E1M10000267H07	3830	S4M10000010D08	5072	S1M10000027G05
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108	E3M10000012B02	1350	E1M10000125A02	2592	E1M10000267A10	3834	S4M10000010D10	5076	S1M10000027D06
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113	E3M10000012F07	1355	E1M10000120E05	2597	E1M10000267E12	3839	S4M10000011E10	5081	S1M10000027B07
114	E3M10000012G07	1356	E1M10000120A06	2598	E1M10000268F03	3840	S4M10000011F10	5082	S1M10000027D07
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117	E3M10000012F10	1359	E1M10000120G10	2601	E1M10000268F06	3843	S4M10000012B06	5085	S1M10000027H07
118	E3M10000013D02	1360	E1M10000136C01	2602	E1M10000268E07	3844	S4M10000012B12	5086	S1M10000027A08
119	E3M10000013E02	1361	E1M10000136H01	2603	E1M10000268A08	3845	S4M10000013D02	5087	S1M10000027B08
120	E3M10000013H03	1362	E1M10000136E02	2604	E1M10000268B08	3846	S4M10000013H02	5088	S1M10000027C08
121	E3M10000013C05	1363	E1M10000136B03	2605	E1M10000268D08	3847	S4M10000014H02	5089	S1M10000027D08
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123	E3M10000013H05	1365	E1M10000121D01	2607	E1M10000268B09	3849	S4M10000014D07	5091	S1M10000027F08
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126	E3M10000013D08	1368	E1M10000121E07	2610	E1M10000268G09	3852	S4M10000016A02	5094	S1M10000027B09
127	E3M10000013E08	1369	E1M10000121D08	2611	E1M10000268E10	3853	S4M10000020F08	5095	S1M10000027C09
128	E3M10000013D10	1370	E1M10000129G04	2612	E1M10000268A11	3854	S4M10000021E07	5096	S1M10000027D09
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130	E3M10000014G09	1372	E1M10000129F11	2614	E1M10000268G12	3856	S4M10000022D04	5098	S1M10000027F09
131	E3M10000014B12	1373	E1M10000126E08	2615	E1M10000269D01	3857	S4M10000022B05	5099	S1M10000027G09
132	E3M10000014E12	1374	E1M10000126F12	2616	E1M10000269B02	3858	S4M10000022G07	5100	S1M10000027H09
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136	E3M10000016A03	1378	E1M10000137C03	2620	E1M10000269B05	3862	S4M10000024G04	5104	S1M10000027B11
137	E3M10000016D03	1379	E1M10000137C04	2621	E1M10000269D05	3863	S4M10000024C06	5105	S1M10000027D11
138	E3M10000016A04	1380	E1M10000137E07	2622	E1M10000269H05	3864	S4M10000024F08	5106	S1M10000027E11
139	E3M10000016G05	1381	E1M10000137B08	2623	E1M10000269A06	3865	S4M10000024G09	5107	S1M10000027G11
140	E3M10000016H05	1382	E1M10000137G09	2624	E1M10000269E07	3866	S4M10000024C11	5108	S1M10000027H11
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144	E3M10000017A09	1386	E1M10000139B11	2628	E1M10000269C12	3870	S4M10000025A11	5112	S1M10000028G01
145	E3M10000017D09	1387	E1M10000140B05	2629	E1M10000269G12	3871	S4M10000025F12	5113	S1M10000028A02
146	E3M10000018E01	1388	E1M10000142H03	2630	E1M10000271F02	3872	S4M10000026C01	5114	S1M10000028B02
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161	E3M10000021A08	1403	E1M10000155B05	2645	E1M10000272G03	3887	S4M10000034C05	5129	S1M10000028G04
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176	E3M10000022C06	1418	E1M10000153H03	2660	E1M10000273H03	3902	S4M10000037A08	5144	S1M10000028H07
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284	E3M10000028D06	1526	E1M10000187F11	2768	E1M10000314G10	4010	S1M10000004F02	5252	S1M10000030G11
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320	E3M10000029G05	1562	E1M10000192D10	2804	E1M10000317C01	4046	S1M10000004E12	5288	S1M10000031A10
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374	E3M10000030F06	1616	E1M10000196B02	2858	E1M10000280H09	4100	S1M10000006G04	5342	S1M10000032E09
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392	E3M10000030E10	1634	E1M10000196D12	2876	E1M10000282D01	4118	S1M10000006C10	5360	S1M10000032G12
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536	E3M10000033F08	1778	E1M10000208F08	3020	E1M10000286D01	4262	S1M10000011A04	5504	S1M10000035E12
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648	E3M10000036H03	1890	E1M10000215F01	3132	E1M10000291F08	4374	S1M10000013F10	5616	S1M10000038C01
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676	E3M10000036A09	1918	E1M10000216E05	3160	E1M10000293F11	4402	S1M10000014H04	5644	S1M10000038H07
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684	E3M10000036D10	1926	E1M10000216D12	3168	E1M10000295H04	4410	S1M10000014C06	5652	S1M10000038B09
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687	E3M10000036H10	1929	E1M10000217H02	3171	E1M10000295C07	4413	S1M10000014H06	5655	S1M10000038H09
688	E3M10000036B11	1930	E1M10000217C04	3172	E1M10000295D08	4414	S1M10000014A07	5656	S1M10000038C10
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720	E3M10000037B07	1962	E1M10000219C06	3204	E1M10000296B11	4446	S1M10000015G01	5688	S1M10000039F05
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734	E3M10000037G10	1976	E1M10000220A03	3218	E1M10000298C06	4460	S1M10000015A04	5702	S1M10000039F08
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893	E3M10000040F11	2135	E1M10000237H07	3377	E1M10000285E11	4619	S1M10000018A05	5861	S1M10000043B01
894	E3M10000040G11	2136	E1M10000237A08	3378	E1M10000285F11	4620	S1M10000018B05	5862	S1M10000043D01
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901	E3M10000041B02	2143	E1M10000238G01	3385	E1M10000289G12	4627	S1M10000018F07	5869	S1M10000043D02
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932	E3M10000041A08	2174	E1M10000239G11	3416	K1M10000019D06	4658	S1M10000018E12	5900	S1M10000043E10
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936	E3M10000041F08	2178	E1M10000240A04	3420	K1M10000030C04	4662	S1M10000019C01	5904	S1M10000043C11
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939	E3M10000041A09	2181	E1M10000240C08	3423	K1M10000032E11	4665	S1M10000019F01	5907	S1M10000043A12
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941	E3M10000041C09	2183	E1M10000240B10	3425	K1M10000033B02	4667	S1M10000019D02	5909	S1M10000043C12
942	E3M10000041D09	2184	E1M10000240B11	3426	K1M10000037D10	4668	S1M10000019E02	5910	S1M10000043D12
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968	E3M10000042A02	2210	E1M10000243F03	3452	P1M10000026F04	4694	S1M10000019F08	5936	S1M10000044B08
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977	E3M10000042E05	2219	E1M10000243E11	3461	P1M10000028E02	4703	S1M10000019G10	5945	S1M10000044H09
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1014	E3M10000043G04	2256	E1M10000245C11	3498	P1M10000044F07	4740	S1M10000020A08	5982	S1M10000045C07
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1020	E3M10000043H06	2262	E1M10000245E12	3504	P1M10000047H02	4746	S1M10000020C09	5988	S1M10000045F08
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1040	E3M10000043G10	2282	E1M10000247E02	3524	P1M10000055A11	4766	S1M10000021G01	6008	S1M10000045E12
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1073	E3M10000050D06	2315	E1M10000249D06	3557	P1M10000065C03	4799	S1M10000021D09	6041	S1M10000046E07
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1075	E3M10000050H06	2317	E1M10000249C07	3559	P1M10000065C05	4801	S1M10000021F09	6043	S1M10000046A08
1076	E3M10000050A07	2318	E1M10000249B08	3560	P1M10000065D06	4802	S1M10000021A10	6044	S1M10000046B08
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1081	E3M10000050H07	2323	E1M10000249E10	3565	P1M10000066A10	4807	S1M10000021F11	6049	S1M10000046A09
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1089	E3M10000050H09	2331	E1M10000250E04	3573	P1M10000067G05	4815	S1M10000022C02	6057	S1M10000046G10
1090	E3M10000050B10	2332	E1M10000250H04	3574	P1M10000067A06	4816	S1M10000022A03	6058	S1M10000046H10
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1093	E3M10000051C03	2335	E1M10000250G07	3577	P1M10000068G01	4819	S1M10000022D03	6061	S1M10000046C11
1094	E3M10000051D03	2336	E1M10000250D09	3578	P1M10000068D04	4820	S1M10000022E03	6062	S1M10000046D11
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1109	E3M10000051A08	2351	E1M10000251H08	3593	P1M10000070B10	4835	S1M10000022H06	6077	S1M10000047G02
1110	E3M10000051B08	2352	E1M10000251H09	3594	P1M10000070G12	4836	S1M10000022B07	6078	S1M10000047A03
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1116	E3M10000051E09	2358	E1M10000251F12	3600	P1M10000073G03	4842	S1M10000022A08	6084	S1M10000047H03
1117	E3M10000051G09	2359	E1M10000252D01	3601	P1M10000073D04	4843	S1M10000022B08	6085	S1M10000047A04
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1119	E3M10000051A10	2361	E1M10000252C03	3603	P1M10000073D09	4845	S1M10000022D08	6087	S1M10000047C04
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1127	E3M10000051E11	2369	E1M10000252A07	3611	P1M10000075F02	4853	S1M10000022C11	6095	S1M10000047C05
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1135	E3M10000050D03	2377	E1M10000252E12	3619	P1M10000076D10	4861	S1M10000023D01	6103	S1M10000047C06
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1140	E3M10000052C01	2382	E1M10000253F04	3624	P1M10000096F01	4866	S1M10000023H02	6108	S1M10000047C07
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1146	E3M10000052E03	2388	E1M10000253E09	3630	P1M10000059H09	4872	S1M10000023F04	6114	S1M10000047B08
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1148	E3M10000052B04	2390	E1M10000253G09	3632	P1M10000059B11	4874	S1M10000023D05	6116	S1M10000047E08
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1157	E3M10000052B07	2399	E1M10000254B03	3641	P1M10000079C10	4883	S1M10000023H07	6125	S1M10000047F09
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1163	E3M10000052D12	2405	E1M10000254B06	3647	P1M10000080C06	4889	S1M10000023B09	6131	S1M10000047E10
1164	1008-H20	2406	E1M10000254A07	3648	P1M10000081G05	4890	S1M10000023D09	6132	S1M10000047F10
1165	1011-P20	2407	E1M10000254E07	3649	P1M10000081H05	4891	S1M10000023G09	6133	S1M10000047G10
1166	1053-37	2408	E1M10000254G07	3650	P1M10000081A06	4892	S1M10000023H09	6134	S1M10000047H10
1167	1010-C11	2409	E1M10000254A08	3651	P1M10000081D12	4893	S1M10000023B10	6135	S1M10000047A11
1168	1017-H1	2410	E1M10000254B09	3652	P1M10000082A02	4894	S1M10000023C10	6136	S1M10000047B11
1169	1067-16	2411	E1M10000254F10	3653	P1M10000082B04	4895	S1M10000023D10	6137	S1M10000047C11
1170	1083-27	2412	E1M10000254A11	3654	P1M10000082A05	4896	S1M10000023E10	6138	S1M10000047E11
1171	1065-12	2413	E1M10000254C11	3655	P1M10000082C05	4897	S1M10000023F10	6139	S1M10000047F11
1172	221-41	2414	E1M10000254E12	3656	P1M10000082D05	4898	S1M10000023H10	6140	S1M10000047H11
1173	B17-6.O10	2415	E1M10000255C01	3657	P1M10000082E05	4899	S1M10000023A11	6141	S1M10000047A12
1174	910-B20	2416	E1M10000255G02	3658	P1M10000083B01	4900	S1M10000023B11	6142	S1M10000047B12
1175	B18-2.N21	2417	E1M10000255H02	3659	P1M10000083A11	4901	S1M10000023C11	6143	S1M10000047C12
1176	971-B20	2418	E1M10000255A04	3660	P1M10000083B12	4902	S1M10000023E11	6144	S1M10000047D12
1177	D1-1.A15	2419	E1M10000255D05	3661	P1M10000083C12	4903	S1M10000023F11	6145	S1M10000047E12
1178	4-28.1	2420	E1M10000255F06	3662	P1M10000084D03	4904	S1M10000023G11	6146	S1M10000047F12
1179	D1-2.B13	2421	E1M10000255G06	3663	P1M10000084A04	4905	S1M10000023A12	6147	S1M10000048C01
1180	D1-2.P21	2422	E1M10000255B08	3664	P1M10000084E04	4906	S1M10000023B12	6148	S1M10000048D01
1181	Z.56-D2	2423	E1M10000255D09	3665	P1M10000084F08	4907	S1M10000023C12	6149	S1M10000048G01
1182	PJMF55	2424	E1M10000255F09	3666	P1M10000084E11	4908	S1M10000023D12	6150	S1M10000048H01
1183	R1-15.A13	2425	E1M10000255B10	3667	P1M10000085D06	4909	S1M10000023F12	6151	S1M10000048A02
1184	R1-19.H1	2426	E1M10000256F01	3668	P1M10000086B01	4910	S1M10000024D01	6152	S1M10000048B02
1185	R1-55.M2	2427	E1M10000256B02	3669	P1M10000086E01	4911	S1M10000024A02	6153	S1M10000048C02

SeqID	Clone Name	SeqID	Clone Name	SeqID	Clone Name	SeqID	Clone Name	SeqID	Clone Name
1186	Z45-F11	2428	E1M10000256D02	3670	P1M10000086A02	4912	S1M10000024C02	6154	S1M10000048D02
1187	Z8-B9	2429	E1M10000256A04	3671	P1M10000086D02	4913	S1M10000024D02	6155	S1M10000048E02
1188	E1M10000007B04	2430	E1M10000256C05	3672	P1M10000086E05	4914	S1M10000024F02	6156	S1M10000048F02
1189	227-10	2431	E1M10000256E07	3673	P1M10000087E04	4915	S1M10000024H02	6157	S1M10000048G02
1190	709-F23	2432	E1M10000256E09	3674	P1M10000087F04	4916	S1M10000024D03	6158	S1M10000048H02
1191	801-C15	2433	E1M10000256A10	3675	P1M10000087C09	4917	S1M10000024E03	6159	S1M10000048A03
1192	801-H19	2434	E1M10000256F10	3676	P1M10000087F09	4918	S1M10000024F03	6160	S1M10000048B03
1193	804-P6	2435	E1M10000256C12	3677	P1M10000087A11	4919	S1M10000024A04	6161	S1M10000048C03
1194	807-D20	2436	E1M10000257C01	3678	P1M10000088C04	4920	S1M10000024C04	6162	S1M10000048E03
1195	B13-17.G8	2437	E1M10000257G01	3679	P1M10000088A07	4921	S1M10000024D04	6163	S1M10000048F03
1196	B5-6.C8	2438	E1M10000257A02	3680	P1M10000089G08	4922	S1M10000024H04	6164	S1M10000048G03
1197	B8-2.D9	2439	E1M10000257D02	3681	P1M10000089D11	4923	S1M10000024B05	6165	S1M10000048H03
1198	B15-8.P13	2440	E1M10000257H02	3682	P1M10000090E01	4924	S1M10000024E05	6166	S1M10000048E04
1199	T13-5.A2	2441	E1M10000257C03	3683	P1M10000090F06	4925	S1M10000024F05	6167	S1M10000048G04
1200	T12-3.I11	2442	E1M10000257F04	3684	P1M10000090F08	4926	S1M10000024G05	6168	S1M10000048H04
1201	T20-15.D4	2443	E1M10000257G04	3685	P1M10000090B11	4927	S1M10000024B06	6169	S1M10000048A05
1202	T24-15.G6	2444	E1M10000257B05	3686	P1M10000091A09	4928	S1M10000024E06	6170	S1M10000048B05
1203	T24-17.C6	2445	E1M10000257D05	3687	P1M10000091E09	4929	S1M10000024G06	6171	S1M10000048C05
1204	244.B12	2446	E1M10000257F06	3688	P1M10000091G10	4930	S1M10000024H06	6172	S1M10000048F05
1205	1042-J1	2447	E1M10000257G07	3689	P1M10000092B02	4931	S1M10000024A07	6173	S1M10000048G05
1206	195.F5	2448	E1M10000257H07	3690	P1M10000092E02	4932	S1M10000024C07	6174	S1M10000048H05
1207	25.D5	2449	E1M10000257H08	3691	P1M10000092B04	4933	S1M10000024E07	6175	S1M10000048A06
1208	25.D6	2450	E1M10000257A09	3692	P1M10000092F05	4934	S1M10000024G07	6176	S1M10000048B06
1209	177.F3	2451	E1M10000257D09	3693	P1M10000092F06	4935	S1M10000024H07	6177	S1M10000048C06
1210	525.H11	2452	E1M10000257G10	3694	P1M10000092D09	4936	S1M10000024A08	6178	S1M10000048E06
1211	632.N2	2453	E1M10000257H10	3695	P1M10000092B10	4937	S1M10000024B08	6179	S1M10000048A07
1212	633.B7	2454	E1M10000257A11	3696	P1M10000092B12	4938	S1M10000024E08	6180	S1M10000048C07
1213	671.I20	2455	E1M10000257C11	3697	P1M10000093A03	4939	S1M10000024F08	6181	S1M10000048E07
1214	676.B12	2456	E1M10000257F11	3698	P1M10000093B03	4940	S1M10000024G08	6182	S1M10000048F07
1215	643.B19	2457	E1M10000257B12	3699	P1M10000093F03	4941	S1M10000024H08	6183	S1M10000048G07
1216	720.O16	2458	E1M10000257F12	3700	P1M10000093H07	4942	S1M10000024B09	6184	S1M10000048H07
1217	666.H12	2459	E1M10000258C01	3701	P1M10000093C08	4943	S1M10000024B10	6185	S1M10000048B08
1218	98.D4	2460	E1M10000258H02	3702	P1M10000093B09	4944	S1M10000024D10	6186	S1M10000048C08
1219	844.B21	2461	E1M10000258G03	3703	P1M10000093E09	4945	S1M10000024F10	6187	S1M10000048D08
1220	P31-25-F3	2462	E1M10000258A04	3704	P1M10000094H03	4946	S1M10000024G10	6188	S1M10000048E08
1221	P335-8.H8	2463	E1M10000258C04	3705	P1M10000094F04	4947	S1M10000024A11	6189	S1M10000048F08

SeqID	Clone Name	SeqID	Clone Name	SeqID	Clone Name	SeqID	Clone Name	SeqID	Clone Name
1222	P347.2	2464	E1M10000258G04	3706	P1M10000094H04	4948	S1M10000024D11	6190	S1M10000048H08
1223	P31-11-J20	2465	E1M10000258C05	3707	P1M10000094A10	4949	S1M10000024G12	6191	S1M10000048A09
1224	P3.36-14.F20	2466	E1M10000258D05	3708	P1M10000095C01	4950	S1M10000025B01	6192	S1M10000048C09
1225	P31-27-M1	2467	E1M10000258F05	3709	P1M10000095E04	4951	S1M10000025C01	6193	S1M10000048D09
1226	P338-4.M21	2468	E1M10000258G05	3710	P1M10000095G04	4952	S1M10000025D01	6194	S1M10000048E09
1227	P334-8.L7	2469	E1M10000258A06	3711	P1M10000095C09	4953	S1M10000025E01	6195	S1M10000048F09
1228	P31-2-E16	2470	E1M10000258D06	3712	P1M10000102E05	4954	S1M10000025B02	6196	S1M10000048H09
1229	P335-3.J14	2471	E1M10000258B07	3713	P1M10000102B07	4955	S1M10000025A03	6197	S1M10000048A10
1230	P334-5.H2	2472	E1M10000258G07	3714	P1M10000103B05	4956	S1M10000025B03	6198	S1M10000048B10
1231	P31-33-N2	2473	E1M10000258G08	3715	P1M10000103D06	4957	S1M10000025C03	6199	S1M10000048C10
1232	P332-11.C20	2474	E1M10000258B09	3716	P1M10000103E08	4958	S1M10000025D03	6200	S1M10000048D10
1233	869.A23	2475	E1M10000258D09	3717	P1M10000104A02	4959	S1M10000025F03	6201	S1M10000048E10
1234	P317-2.A3	2476	E1M10000258F10	3718	P1M10000104H02	4960	S1M10000025D04	6202	S1M10000048G10
1235	P326-9.K2	2477	E1M10000258C11	3719	P1M10000104A03	4961	S1M10000025E04	6203	S1M10000048H10
1236	P323-8.P1	2478	E1M10000258F11	3720	P1M10000104E03	4962	S1M10000025G04	6204	S1M10000048A11
1237	P35-8	2479	E1M10000259C03	3721	P1M10000104F07	4963	S1M10000025B05	6205	S1M10000048C11
1238	P36-13.E2	2480	E1M10000259B04	3722	P1M10000104D11	4964	S1M10000025C05	6206	S1M10000048D11
1239	P38-1.G20	2481	E1M10000259E04	3723	P1M10000105D01	4965	S1M10000025F05	6207	S1M10000048F11
1240	P327-50.M10	2482	E1M10000259E05	3724	P1M10000105E02	4966	S1M10000025H05	6208	S1M10000048G11
1241	P328-8.D21	2483	E1M10000259B12	3725	P1M10000105C03	4967	S1M10000025B06	6209	S1M10000048H11
1242	P328-20.P20	2484	E1M10000260E02	3726	P1M10000105G03	4968	S1M10000025D06	6210	S1M10000048A12

EXAMPLE 3

Comparison Of Isolated Nucleic Acids to Known Sequences

The nucleotide sequences of the subcloned fragments from *Escherichia coli, Staphylococcus aureus, Enterococcus faecalis, Klebsiella pneumoniae, Pseudomonas aeruginosa* and *Salmonella*

5 *typhimurium* obtained from the expression vectors discussed above were compared to known sequences from *Escherichia coli, Staphylococcus aureus, Enterococcus faecalis, Klebsiella pneumoniae, Pseudomonas aeruginosa, Salmonella typhimurium* and other microorganisms as follows. First, to confirm that each clone originated from one location on the chromosome and was not chimeric, the nucleotide sequences of the selected clones were compared against the

10 *Escherichia coli, Staphylococcus aureus, Enterococcus faecalis, Klebsiella pneumoniae, Pseudomonas aeruginosa* or *Salmonella typhimurium* genomic sequences to align the clone to the correct position on the chromosome. The NCBI BLASTN v 2.0.9 program was used for this comparison, and the incomplete *Staphylococcus aureus* genomic sequences licensed from TIGR, as well as the NCBI nonredundant GenBank database were used as the source of genomic data.

15 *Salmonella typhimurium* sequences were compared to sequences available from the Genome Sequencing Center (http://genome.wustl.edu/gsc/salmonella.shtml), and the Sanger Centre (http://www.sanger.ac.uk/projects/S___typhi). *Pseudomonas aeruginosa* sequences were compared to a proprietary database and the NCBI GenBank database. The *E. faecalis* sequences were compared to a proprietary database.

20 The BLASTN analysis was performed using the default parameters except that the filtering was turned off. No further analysis was performed on inserts which resulted from the ligation of multiple fragments.

In general, antisense molecules and their complementary genes are identified as follows. First, all possible full length open reading frames (ORFs) are extracted from available genomic

25 databases. Such databases include the GenBank nonredundant (nr) database, the unfinished genome database available from TIGR and the PathoSeq database developed by Incyte Genomics. The latter database comprises over 40 annotated bacterial genomes including complete ORF analysis. If databases are incomplete with regard to the bacterial genome of interest, it is not necessary to extract all ORFs in the genome but only to extract the ORFs within the portions of the

30 available genomic sequences which are complementary to the clones of interest. Computer algorithms for identifying ORFs, such as GeneMark, are available and well known to those in the art. Comparison of the clone DNA to the complementary ORF(s) allows determination of whether the clone is a sense or antisense clone. Furthermore, each ORF extracted from the database can be compared to sequences in well annotated databases including the GenBank (nr) protein database,

35 SWISSPROT and the like. A description of the gene or of a closely related gene in a closely related microorganism is often available in these databases. Similar methods are used to identify antisense clones corresponding to genes encoding non-translated RNAs.

In order to generate the gene identification data compiled in Table IB, each of the cloned nucleic acid sequences discussed above corresponding to SEQ ID NO.s 1-6213 was used to identify the corresponding *Escherichia coli, Staphylococcus aureus, Enterococcus faecalis, Klebsiella pneumoniae, Pseudomonas aeruginosa* or *Salmonella typhimurium* ORFs in the PathoSeq v.4.1

5   (March 2000 release) database of microbial genomic sequences. For this purpose, the NCBI BLASTN 2.0.9 computer algorithm was used. The default parameters were used except that filtering was turned off. The default parameters for the BLASTN and BLASTX analyses were:

Expectation value (e)=10

Alignment view options: pairwise
10   Filter query sequence (DUST with BLASTN, SEG with others)=T
Cost to open a gap (zero invokes behavior)=0
Cost to extend a gap (zero invokes behavior)=0
X dropoff value for gapped alignment (in bits) (zero invokes behavior)=0
Show GI's in deflines=F
15   Penalty for a nucleotide mismatch (BLASTN only)=!3
Reward for a nucleotide match (BLASTN only)=1
Number of one-line descriptions (V)=500
Number of alignments to show (B)=250
Threshold for extending hits=default
20   Perform gapped alignment (not available with BLASTX)=T
Query Genetic code to use=1
DB Genetic code (for TBLAST[nx] only=1
Number of processors to use=1
SeqAlign file
25   Believe the query defline=F
Matrix=BLOSUM62
Word Size= default
Effective length of the database (use zero for the real size)=0
Number of best hits from a region to keep=100
30   Length of region used to judge hits=20
Effective length of the search space (use zero for the real size)=0
Query strands to search against database (for BLAST[nx] and TBLASTX), 3 is both, 1 is top, 2 is bottom=3
Produce HTML output=F

35

Alternatively, ORFs were identified and refined by conducting a survey of the public and private data sources. Full-length gene protein and nucleotide sequences for these organisms were assembled from various sources. For *Pseudomonas aeruginosa*, gene sequences were adopted from the Pseudomonas genome sequencing project (downloaded from http://www.pseudomonas.com).

40   For *Klebsiella pneumoniae, Staphylococcus aureus, Streptococcus pneumoniae* and *Salmonella typhi*, genomic sequences from PathoSeq v 4.1 (Mar 2000 release) was reanalyzed for ORFs using the gene finding software GeneMark v 2.4a, which was purchased from GenePro Inc. 451 Bishop St., N.W., Suite B, Atlanta, GA, 30318, USA.

Antisense clones were identified as those clones for which transcription from the inducible
45   promoter would result in the expression of an RNA antisense to a complementary ORF, intergenic

or intragenic sequence. Those clones containing single inserts and that caused growth sensitivity upon induction are listed in Table IA.

The gene descriptions in the PathoSeq database derive from annotations available in the public sequence databases described above. Where a clone was found to share significant sequence identity to two or more adjacent ORFs, it was listed once for each ORF and the PathoSeq information for each ORF was compiled in Table IB.

Table IA lists the SEQ ID NOs. and clone names of the inserts which inhibited proliferation. This information was used to identify the ORFs (SEQ ID NOs.: 6214-42397) whose gene products (SEQ ID NOs. 42398-78581) were inhibited by the nucleic acids comprising the nucleotide sequences of SEQ ID NOs. 1-6213. Table IB lists the clone name and the PathoSeq Locus containing the clone.

TABLE IB

Clone Name	Gene LocusID	Clone Name	Gene LocusID	Clone Name	Gene LocusID
E3M10000001B01	EFA205257	E1M10000233C05	ECO103161	S1M10000005E05	SAU802496
E3M10000001B01	EFA205258	E1M10000233H05	ECO103224	S1M10000005C06	SAU802121
E3M10000001A02	EFA205257	E1M10000233H05	ECO103225	S1M10000005D06	SAU801183
E3M10000001A02	EFA205258	E1M10000233D08	ECO103185	S1M10000005D06	SAU801184
E3M10000001B02	EFA205225	E1M10000233F08	ECO103265	S1M10000005A07	SAU800967
E3M10000001B02	EFA201977	E1M10000233F08	ECO103266	S1M10000005B07	SAU802496
E3M10000001B02	EFA203137	E1M10000233A09	ECO104092	S1M10000005D07	SAU801264
E3M10000001C02	EFA200840	E1M10000233A09	ECO104093	S1M10000005A08	SAU802496
E3M10000001D02	EFA202003	E1M10000233E09	ECO103238	S1M10000005B08	SAU800548
E3M10000001E02	EFA200840	E1M10000233E09	ECO103239	S1M10000005D08	SAU800607
E3M10000001F02	EFA200807	E1M10000233F09	ECO103886	S1M10000005E08	SAU802496
E3M10000001G02	EFA205257	E1M10000233D10	ECO103242	S1M10000005B09	SAU800122
E3M10000001G02	EFA205258	E1M10000233D10	ECO103243	S1M10000005C09	SAU801481
E3M10000001H02	EFA200811	E1M10000233H10	ECO100094	S1M10000005D09	SAU800542
E3M10000001E03	EFA201987	E1M10000234E01	ECO103884	S1M10000005A10	SAU801723
E3M10000001E03	EFA205258	E1M10000234B02	ECO103886	S1M10000005A10	SAU801722
E3M10000001G03	EFA201987	E1M10000234G02	ECO103233	S1M10000005A11	SAU801644
E3M10000001G03	EFA205258	E1M10000234G02	ECO103234	S1M10000005C11	SAU801113
E3M10000001H03	EFA201987	E1M10000234C05	ECO103181	S1M10000005D11	SAU800547
E3M10000001H03	EFA205258	E1M10000234C07	ECO103844	S1M10000005E11	SAU800155
E3M10000001D04	EFA201980	E1M10000234C08	ECO103878	S1M10000005B12	SAU802160
E3M10000001D04	EFA201981	E1M10000234C08	ECO204942	S1M10000005B12	SAU603460
E3M10000001D04	EFA205229	E1M10000234F08	ECO103461	S1M10000005D12	SAU801644
E3M10000001E04	EFA201028	E1M10000234H08	ECO103226	S1M10000006F01	SAU801264
E3M10000001F04	EFA200811	E1M10000234F09	ECO103055	S1M10000006B02	SAU800381
E3M10000001G04	EFA201993	E1M10000234D10	ECO100876	S1M10000006E02	SAU802496
E3M10000001H04	EFA201980	E1M10000234G10	ECO100886	S1M10000006F02	SAU802160
E3M10000001H04	EFA201981	E1M10000234B12	ECO104010	S1M10000006G02	SAU802125
E3M10000001H04	EFA205229	E1M10000235D01	ECO102233	S1M10000006A03	SAU802496
E3M10000001B05	EFA201993	E1M10000235A03	ECO100798	S1M10000006B03	SAU802655
E3M10000001D05	EFA201974	E1M10000235H03	ECO103886	S1M10000006D03	SAU801740
E3M10000001D05	EFA201975	E1M10000235E04	ECO103236	S1M10000006E03	SAU801256
E3M10000001G05	EFA202001	E1M10000235B06	ECO103886	S1M10000006F03	SAU801434
E3M10000001G05	EFA202003	E1M10000235F06	ECO103481	S1M10000006G03	SAU801275
E3M10000001A06	EFA201028	E1M10000235B08	ECO103885	S1M10000006A04	SAU801139
E3M10000001F06	EFA201028	E1M10000235E08	ECO103161	S1M10000006B04	SAU802496
E3M10000001B08	EFA201028	E1M10000235B09	ECO101848	S1M10000006C04	SAU802158
E3M10000001E08	EFA200807	E1M10000235H09	ECO103481	S1M10000006E04	SAU801089
E3M10000001C09	EFA200839	E1M10000235H09	ECO103482	S1M10000006F04	SAU801644
E3M10000001D09	EFA201987	E1M10000235B10	ECO100886	S1M10000006G04	SAU801740
E3M10000001D09	EFA205258	E1M10000235A11	ECO102299	S1M10000006A05	SAU802224
E3M10000001E09	EFA201987	E1M10000235F12	ECO103233	S1M10000006A05	SAU802223
E3M10000001E09	EFA205258	E1M10000235F12	ECO103234	S1M10000006D05	SAU802496
E3M10000001B10	EFA205257	E1M10000236E01	ECO100095	S1M10000006G05	SAU801256
E3M10000001B10	EFA205258	E1M10000236A02	ECO102340	S1M10000006C06	SAU800331
E3M10000004D01	EFA201985	E1M10000236F02	ECO103878	S1M10000006C06	SAU800332
E3M10000004D01	EFA201984	E1M10000236E02	ECO204942	S1M10000006D06	SAU802496
E3M10000004D01	EFA202953	E1M10000236A03	ECO103287	S1M10000006F06	SAU800548
E3M10000004G01	EFA200839	E1M10000236D03	ECO102556	S1M10000006G06	SAU800006
E3M10000004D02	EFA202022	E1M10000236G03	ECO102655	S1M10000006A07	SAU800967
E3M10000004D02	EFA202028	E1M10000236A04	ECO103186	S1M10000006B07	SAU801760

Clone Name	Gene LocusID	Clone Name	Gene LocusID	Clone Name	Gene LocusID
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E3M10000033F12	EFA200812	E1M10000269D01	ECO103232	S1M10000018B10	SAU801554
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221-41	ECO103884	E1M10000293E05	ECO103224	S1M10000030C05	SAU800526
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910-B20	ECO103884	E1M10000293A06	ECO101175	S1M10000030D05	SAU302793
B18-2.N21	ECO100148	E1M10000293H06	ECO102654	S1M10000030G05	SAU800776
971-B20	ECO103240	E1M10000293F07	ECO101095	S1M10000030G05	SAU800777
971-B20	ECO103241	E1M10000293C08	ECO101844	S1M10000030H05	SAU800179
D1-1.A15	ECO103394	E1M10000293E08	ECO101939	S1M10000030D06	SAU800189
4-28.1	ECO101485	E1M10000293G08	ECO103101	S1M10000030E06	SAU801257
D1-2.B13	ECO102255	E1M10000293B09	ECO103181	S1M10000030B07	SAU802627
D1-2.P21	ECO102144	E1M10000293G09	ECO102144	S1M10000030D07	SAU800189
Z56-D2	ECO103911	E1M10000293H09	ECO100094	S1M10000030G07	SAU802247
PJMF55	ECO103264	E1M10000293H09	ECO100095	S1M10000030H07	SAU800525
PJMF55	ECO103265	E1M10000293A11	ECO103883	S1M10000030C08	SAU801831
R1-15.A13	ECO101995	E1M10000293E11	ECO103242	S1M10000030F08	SAU802231
R1-19.H1	ECO101104	E1M10000293F11	ECO104091	S1M10000030F08	SAU802230
R1-55.M2	ECO103884	E1M10000293F11	ECO104092	S1M10000030G08	SAU802250
Z45-F11	ECO103263	E1M10000293C12	ECO100170	S1M10000030A09	SAU801719
Z8-B9	ECO102033	E1M10000293D12	ECO103221	S1M10000030B09	SAU802654
E1M10000007B04	ECO102986	E1M10000295D01	ECO103228	S1M10000030C09	SAU800542
227-10	ECO102562	E1M10000295D01	ECO103229	S1M10000030D09	SAU801139
709-F23	ECO101506	E1M10000295G01	ECO103532	S1M10000030F09	SAU801904
801-C15	ECO100488	E1M10000295G01	ECO103533	S1M10000030G09	SAU800542
801-C15	ECO100490	E1M10000295B02	ECO101635	S1M10000030H09	SAU801644
801-C15	ECO100491	E1M10000295E02	ECO103217	S1M10000030A10	SAU802309
801-H19	ECO100488	E1M10000295E02	ECO103218	S1M10000030A10	SAU802308
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804-P6	ECO102513	E1M10000295A07	ECO100712	S1M10000030F10	SAU800019
807-D20	ECO100366	E1M10000295B07	ECO100179	S1M10000030G10	SAU800019
807-D20	ECO100367	E1M10000295B07	ECO100180	S1M10000030H10	SAU802654
B13-17.G8	ECO101111	E1M10000295C07	ECO103224	S1M10000030A11	SAU800517
B5-6.C8	ECO101475	E1M10000295C07	ECO103225	S1M10000030A11	SAU202623
B5-6.C8	ECO101476	E1M10000295C07	ECO103226	S1M10000030D11	SAU800517
B5-6.C8	ECO201962	E1M10000295D08	ECO103225	S1M10000030D11	SAU202623
B8-2.D9	ECO103461	E1M10000295D08	ECO103226	S1M10000030E11	SAU802241
B15-8.P13	ECO101328	E1M10000295F08	ECO103160	S1M10000030G11	SAU800811
B15-8.P13	ECO101329	E1M10000295G08	ECO103217	S1M10000030C12	SAU801647
T13-5.A2	ECO103059	E1M10000295G08	ECO103218	S1M10000030C12	SAU801646
T12-3.I11	ECO102857	E1M10000295B09	ECO103236	S1M10000030E12	SAU800537
T20-15.D4	ECO101475	E1M10000295F09	ECO103881	S1M10000030G12	SAU801526
T20-15.D4	ECO101476	E1M10000295F09	ECO103882	S1M10000031B01	SAU802240
T20-15.D4	ECO201962	E1M10000295G09	ECO103263	S1M10000031H01	SAU800023
T24-15.G6	ECO103059	E1M10000295D10	ECO103101	S1M10000031B02	SAU802247
T24-17.C6	ECO102857	E1M10000295H10	ECO103263	S1M10000031E02	SAU801912
244.B12	ECO101763	E1M10000295B11	ECO103229	S1M10000031F02	SAU802231
244.B12	ECO101764	E1M10000295F11	ECO100954	S1M10000031F02	SAU802230
244.B12	ECO101765	E1M10000295G12	ECO103494	S1M10000031G02	SAU802235
1042-J1	ECO100702	E1M10000312D11	ECO104091	S1M10000031G02	SAU802234
1042-J1	ECO100703	E1M10000312D11	ECO104092	S1M10000031H02	SAU801355
195.F5	ECO102842	E1M10000296B01	ECO102304	S1M10000031A03	SAU802250
25.D5	ECO103059	E1M10000296C02	ECO102466	S1M10000031E03	SAU801134
25.D6	ECO103059	E1M10000296C02	ECO102467	S1M10000031E03	SAU801135
177.F3	ECO102309	E1M10000296D02	ECO103235	S1M10000031F03	SAU802240
525.H11	ECO102857	E1M10000296D02	ECO103236	S1M10000031G03	SAU801505
632.N2	ECO104277	E1M10000296D02	ECO103237	S1M10000031A04	SAU801434
633.B7	ECO103479	E1M10000296H02	ECO102556	S1M10000031A04	SAU302892
671.I20	ECO103478	E1M10000296C03	ECO100150	S1M10000031B04	SAU800543
676.B12	ECO103479	E1M10000296C03	ECO100151	S1M10000031C04	SAU800738
643.B19	ECO100702	E1M10000296E03	ECO101086	S1M10000031C04	SAU800737
720.O16	ECO103884	E1M10000296H03	ECO103227	S1M10000031E04	SAU800542
666.H12	ECO103478	E1M10000296H03	ECO103228	S1M10000031F04	SAU801517
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98.D4	ECO103263	E1M10000296G04	ECO102144	S1M10000031G04	SAU302611
844.B21	ECO102144	E1M10000296F05	ECO103886	S1M10000031G04	SAU302882
P31-25-F3	ECO101686	E1M10000296G05	ECO101467	S1M10000031F05	SAU800548
P335-8.H8	ECO101041	E1M10000296H05	ECO103094	S1M10000031D06	SAU801526
P347.2	ECO101086	E1M10000296A06	ECO100194	S1M10000031G06	SAU800548
P31-11-J20	ECO103228	E1M10000296A06	ECO100195	S1M10000031H06	SAU600582
P336-14.F20	ECO101370	E1M10000296G07	ECO102827	S1M10000031C07	SAU801760
P31-27-M1	ECO103423	E1M10000296G07	ECO102828	S1M10000031D07	SAU801181
P338-4.M21	ECO100139	E1M10000296H07	ECO103220	S1M10000031E07	SAU800016
P334-8.L7	ECO101256	E1M10000296H07	ECO103221	S1M10000031A08	SAU802365
P31-2-E16	ECO101686	E1M10000296E08	ECO100886	S1M10000031D08	SAU801790
P335-3.J14	ECO100523	E1M10000296F08	ECO103218	S1M10000031E08	SAU800547
P334-5.H2	ECO100139	E1M10000296G08	ECO103734	S1M10000031F08	SAU801264
P31-33-N2	ECO103241	E1M10000296H08	ECO100809	S1M10000031C09	SAU801193
P332-11.C20	ECO102827	E1M10000296H08	ECO100810	S1M10000031D09	SAU800019
P332-11.C20	ECO102828	E1M10000296A09	ECO100194	S1M10000031G09	SAU800006
869.A23	ECO100390	E1M10000296B11	ECO103229	S1M10000031H09	SAU801599

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P317-2.A3	ECO101932	E1M10000296B11	ECO103230	S1M10000031A10	SAU800772
P326-9.K2	ECO103292	E1M10000296E11	ECO101684	S1M10000031C10	SAU802654
P326-9.K2	ECO103293	E1M10000296F12	ECO101684	S1M10000031E10	SAU800001
P323-8.P1	ECO101685	E1M10000296G12	ECO100095	S1M10000031F10	SAU800244
P35-8	ECO103692	E1M10000298C01	ECO101438	S1M10000031G10	SAU800962
P36-13.E2	ECO103059	E1M10000298G01	ECO104148	S1M10000031A11	SAU801741
P38-1.G20	ECO102227	E1M10000298G01	ECO104149	S1M10000031B11	SAU801908
P327-50.M10	ECO103242	E1M10000298G02	ECO102636	S1M10000031C11	SAU802152
P327-50.M10	ECO103243	E1M10000298C03	ECO103238	S1M10000031F11	SAU800312
P328-8.D21	ECO103240	E1M10000298C03	ECO103239	S1M10000031G11	SAU801234
P328-8.D21	ECO103241	E1M10000298D03	ECO103886	S1M10000031H11	SAU800962
P328-20.P20	ECO100541	E1M10000298H03	ECO103262	S1M10000031B12	SAU801621
P33-1.C22	ECO103227	E1M10000298H03	ECO103878	S1M10000031C12	SAU801741
X3S107-17	ECO101475	E1M10000298H03	ECO204942	S1M10000031E12	SAU801275
X3S107-17	ECO101476	E1M10000298E04	ECO100430	S1M10000031F12	SAU800244
X3S107-17	ECO201962	E1M10000298E04	ECO100431	S1M10000032B01	SAU802654
P35-7	ECO103928	E1M10000298H04	ECO100809	S1M10000032C01	SAU800548
X3S118-9	ECO103263	E1M10000298H04	ECO100808	S1M10000032F01	SAU800525
X3S163-1	ECO103423	E1M10000298C05	ECO103234	S1M10000032F01	SAU800524
X3S204-7	ECO103238	E1M10000298C05	ECO103235	S1M10000032H01	SAU802112
X3S177-4	ECO101161	E1M10000298C05	ECO103236	S1M10000032H01	SAU802111
P342-3	ECO102104	E1M10000298D05	ECO101539	S1M10000032E02	SAU801096
SC21.1	ECO103224	E1M10000298D05	ECO101540	S1M10000032G02	SAU800830
SC17.1	ECO102087	E1M10000298C06	ECO101844	S1M10000032G02	SAU800829
SC13.1	ECO101347	E1M10000298D06	ECO103886	S1M10000032A03	SAU802686
SC13.1	ECO101348	E1M10000298G06	ECO100096	S1M10000032C03	SAU800771
MC9.6	ECO102929	E1M10000298B07	ECO100095	S1M10000032D03	SAU801235
MC9.6	ECO102928	E1M10000298C07	ECO102638	S1M10000032E03	SAU802240
Z60-P16	ECO103243	E1M10000298G07	ECO103233	S1M10000032G03	SAU801269
Z86-I21	ECO103884	E1M10000298G07	ECO103234	S1M10000032C04	SAU800771
E1M10000109A02	ECO104168	E1M10000298B09	ECO103244	S1M10000032E04	SAU801526
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E1M10000187A10	ECO104214	P1M10000033D06	PAE203004	S1M10000037A11	SAU802292
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E1M10000187G11	ECO101476	P1M10000037B12	PAE204252	S1M10000037D12	SAU800526
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E1M10000189A04	ECO103624	P1M10000038B08	PAE204067	S1M10000038D02	SAU801392
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E1M10000189G10	ECO100148	P1M10000040C01	PAE204103	S1M10000038G03	SAU800547
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E1M10000192F11	ECO101698	P1M10000049E08	PAE204270	S1M10000038C10	SAU801694
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E1M10000220B03	ECO101324	S1M10000002D08	SAU801900	S1M10000047G05	SAU801669
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E1M10000233G04	ECO101185	S1M10000005C05	SAU801264		
E1M10000233A05	ECO102553	S1M10000005D05	SAU801644		

Table 1C provides a cross reference between PathoSeq Gene Loci listed in Table 1B and the SEQ ID NOs. of the corresponding PathoSeq polypeptides and the SEQ ID NOs. of the nucleic acids which encode them. The Gene Locus IDs provided in Table 1C each comprise a nine digit alpha-numeric identifier that can be used to determine the organism from which each Gene Locus and corresponding SEQ ID NOs. were identified. Specifically, the first letter of the Gene Locus ID corresponds to the first letter of the genus name of the organism described herein from which the Gene Locus was identified and the second and third letters of the Gene Locus ID correspond to the first two letters of the species name of this organism. For example, the identifier EFA205257 describes a gene locus identified from *Enterococcus faecalis*. In those instances where the three letter identifier is the same for different organisms, the exact identity of the organism which corresponds to the Gene Locus ID can be determined by referring to the organism designation in the sequence listing for the coding nucleic acid or polypeptide SEQ ID NO. that corresponds to the particular Gene Locus ID.

TABLE IC

DNA SeqID	Protein SeqID	Gene LocusID	DNA SeqID	Protein SeqID	Gene LocusID	DNA SeqID	Protein SeqID	Gene LocusID
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6215	42399	EFA205258	18277	54461	CJU100848	30338	66522	PAE203654
6216	42400	EFA205225	18278	54462	CJU100855	30339	66523	PAE203656
6217	42401	EFA201977	18279	54463	CJU100856	30340	66524	PAE203658
6218	42402	EFA203137	18280	54464	CJU100859	30341	66525	PAE203668
6219	42403	EFA200840	18281	54465	CJU100860	30342	66526	PAE203670
6220	42404	EFA202003	18282	54466	CJU100861	30343	66527	PAE203672
6221	42405	EFA200807	18283	54467	CJU100862	30344	66528	PAE203677
6222	42406	EFA200811	18284	54468	CJU100863	30345	66529	PAE203684
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6224	42408	EFA201980	18286	54470	CJU100870	30347	66531	PAE203698
6225	42409	EFA201981	18287	54471	CJU100871	30348	66532	PAE203722
6226	42410	EFA205229	18288	54472	CJU100872	30349	66533	PAE203732
6227	42411	EFA201028	18289	54473	CJU100885	30350	66534	PAE203735
6228	42412	EFA201993	18290	54474	CJU100886	30351	66535	PAE203739
6229	42413	EFA201974	18291	54475	CJU100888	30352	66536	PAE203740
6230	42414	EFA201975	18292	54476	CJU100890	30353	66537	PAE203741
6231	42415	EFA202001	18293	54477	CJU100891	30354	66538	PAE203742
6232	42416	EFA200839	18294	54478	CJU100896	30355	66539	PAE203743
6233	42417	EFA201985	18295	54479	CJU100903	30356	66540	PAE203744
6234	42418	EFA201984	18296	54480	CJU100923	30357	66541	PAE203751
6235	42419	EFA202953	18297	54481	CJU100925	30358	66542	PAE203754
6236	42420	EFA202022	18298	54482	CJU100929	30359	66543	PAE203755
6237	42421	EFA202028	18299	54483	CJU100938	30360	66544	PAE203757
6238	42422	EFA202536	18300	54484	CJU100944	30361	66545	PAE203758
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6240	42424	EFA201999	18302	54486	CJU100955	30363	66547	PAE203766
6241	42425	EFA201997	18303	54487	CJU100961	30364	66548	PAE203774
6242	42426	EFA200624	18304	54488	CJU100965	30365	66549	PAE203796
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6244	42428	EFA200812	18306	54490	CJU100967	30367	66551	PAE203799
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6246	42430	EFA200661	18308	54492	CJU100980	30369	66553	PAE203801
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6248	42432	EFA201982	18310	54494	CJU100983	30371	66555	PAE203812
6249	42433	EFA202214	18311	54495	CJU100987	30372	66556	PAE203813
6250	42434	EFA202216	18312	54496	CJU100989	30373	66557	PAE203820
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6252	42436	EFA200766	18314	54498	CJU100996	30375	66559	PAE203828
6253	42437	EFA200805	18315	54499	CJU100997	30376	66560	PAE203829
6254	42438	EFA201637	18316	54500	CJU100998	30377	66561	PAE203831
6255	42439	EFA201986	18317	54501	CJU100999	30378	66562	PAE203850
6256	42440	EFA205255	18318	54502	CJU101006	30379	66563	PAE203869
6257	42441	EFA200495	18319	54503	CJU101007	30380	66564	PAE203871
6258	42442	EFA104836	18320	54504	CJU101011	30381	66565	PAE203872
6259	42443	EFA201976	18321	54505	CJU101017	30382	66566	PAE203887
6260	42444	EFA201523	18322	54506	CJU101021	30383	66567	PAE203888
6261	42445	EFA202012	18323	54507	CJU101022	30384	66568	PAE203892
6262	42446	EFA202007	18324	54508	CJU101027	30385	66569	PAE203897
6263	42447	EFA200307	18325	54509	CJU101028	30386	66570	PAE203898
6264	42448	EFA201888	18326	54510	CJU101029	30387	66571	PAE203900
6265	42449	EFA205285	18327	54511	CJU101031	30388	66572	PAE203911

DNA SeqID	Protein SeqID	Gene LocusID	DNA SeqID	Protein SeqID	Gene LocusID	DNA SeqID	Protein SeqID	Gene LocusID
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6268	42452	EFA201611	18330	54514	CJU101046	30391	66575	PAE203920
6269	42453	EFA201946	18331	54515	CJU101050	30392	66576	PAE203943
6270	42454	EFA201512	18332	54516	CJU101054	30393	66577	PAE203958
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6272	42456	EFA203140	18334	54518	CJU101065	30395	66579	PAE203973
6273	42457	EFA200544	18335	54519	CJU101068	30396	66580	PAE203980
6274	42458	EFA203904	18336	54520	CJU101072	30397	66581	PAE203984
6275	42459	EFA202006	18337	54521	CJU101074	30398	66582	PAE203993
6276	42460	EFA202298	18338	54522	CJU101075	30399	66583	PAE204001
6277	42461	EFA200326	18339	54523	CJU101080	30400	66584	PAE204004
6278	42462	EFA200662	18340	54524	CJU101081	30401	66585	PAE204008
6279	42463	EFA202217	18341	54525	CJU101082	30402	66586	PAE204019
6280	42464	EFA201869	18342	54526	CJU101094	30403	66587	PAE204027
6281	42465	EFA203598	18343	54527	CJU101100	30404	66588	PAE204031
6282	42466	EFA200894	18344	54528	CJU101103	30405	66589	PAE204040
6283	42467	EFA200613	18345	54529	CJU101106	30406	66590	PAE204042
6284	42468	EFA202166	18346	54530	CJU101107	30407	66591	PAE204048
6285	42469	EFA202168	18347	54531	CJU101113	30408	66592	PAE204049
6286	42470	EFA201087	18348	54532	CJU101117	30409	66593	PAE204050
6287	42471	EFA201084	18349	54533	CJU101119	30410	66594	PAE204051
6288	42472	EFA201883	18350	54534	CJU101120	30411	66595	PAE204052
6289	42473	EFA201905	18351	54535	CJU101121	30412	66596	PAE204053
6290	42474	EFA202015	18352	54536	CJU101122	30413	66597	PAE204077
6291	42475	EFA202274	18353	54537	CJU101125	30414	66598	PAE204079
6292	42476	EFA200916	18354	54538	CJU101127	30415	66599	PAE204081
6293	42477	EFA200179	18355	54539	CJU101129	30416	66600	PAE204082
6294	42478	EFA200358	18356	54540	CJU101130	30417	66601	PAE204094
6295	42479	EFA200747	18357	54541	CJU101131	30418	66602	PAE204095
6296	42480	EFA200746	18358	54542	CJU101133	30419	66603	PAE204110
6297	42481	EFA201379	18359	54543	CJU101134	30420	66604	PAE204125
6298	42482	EFA201163	18360	54544	CJU101140	30421	66605	PAE204133
6299	42483	EFA202160	18361	54545	CJU101143	30422	66606	PAE204135
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6301	42485	EFA202177	18363	54547	CJU101147	30424	66608	PAE204156
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6303	42487	EFA200562	18365	54549	CJU101152	30426	66610	PAE204177
6304	42488	EFA200192	18366	54550	CJU101153	30427	66611	PAE204198
6305	42489	EFA202180	18367	54551	CJU101154	30428	66612	PAE204199
6306	42490	EFA201749	18368	54552	CJU101159	30429	66613	PAE204210
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6308	42492	EFA202378	18370	54554	CJU101173	30431	66615	PAE204230
6309	42493	EFA202013	18371	54555	CJU101174	30432	66616	PAE204232
6310	42494	EFA202200	18372	54556	CJU101178	30433	66617	PAE204236
6311	42495	EFA203606	18373	54557	CJU101182	30434	66618	PAE204237
6312	42496	EFA203607	18374	54558	CJU101186	30435	66619	PAE204238
6313	42497	EFA201926	18375	54559	CJU101188	30436	66620	PAE204239
6314	42498	EFA201460	18376	54560	CJU101194	30437	66621	PAE204240
6315	42499	EFA200538	18377	54561	CJU101195	30438	66622	PAE204258
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6317	42501	EFA200245	18379	54563	CJU101197	30440	66624	PAE204264
6318	42502	EFA200246	18380	54564	CJU101199	30441	66625	PAE204268
6319	42503	EFA200478	18381	54565	CJU101207	30442	66626	PAE204271
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6324	42508	EFA204646	18386	54570	CJU101217	30447	66631	PAE204281
6325	42509	EFA200240	18387	54571	CJU101231	30448	66632	PAE204282
6326	42510	EFA201884	18388	54572	CJU101238	30449	66633	PAE204284
6327	42511	EFA200677	18389	54573	CJU101268	30450	66634	PAE204290
6328	42512	EFA200418	18390	54574	CJU101271	30451	66635	PAE204312
6329	42513	EFA201920	18391	54575	CJU101273	30452	66636	PAE204327
6330	42514	EFA200357	18392	54576	CJU101276	30453	66637	PAE204332
6331	42515	EFA200359	18393	54577	CJU101278	30454	66638	PAE204352
6332	42516	EFA201041	18394	54578	CJU101290	30455	66639	PAE204357
6333	42517	EFA201801	18395	54579	CJU101295	30456	66640	PAE204359
6334	42518	EFA202631	18396	54580	CJU101298	30457	66641	PAE204374
6335	42519	EFA201886	18397	54581	CJU101309	30458	66642	PAE204383
6336	42520	EFA200674	18398	54582	CJU101319	30459	66643	PAE204399
6337	42521	EFA202110	18399	54583	CJU101321	30460	66644	PAE204401
6338	42522	EFA201009	18400	54584	CJU101322	30461	66645	PAE204402
6339	42523	EFA201878	18401	54585	CJU101325	30462	66646	PAE204404
6340	42524	EFA201208	18402	54586	CJU101328	30463	66647	PAE204405
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6357	42541	EFA201025	18419	54603	CJU101426	30480	66664	PAE204442
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6359	42543	EFA201970	18421	54605	CJU101443	30482	66666	PAE204448
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6365	42549	EFA201507	18427	54611	CJU101458	30488	66672	PAE204481
6366	42550	EFA205207	18428	54612	CJU101462	30489	66673	PAE204482
6367	42551	EFA203246	18429	54613	CJU101467	30490	66674	PAE204487
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6369	42553	EFA200590	18431	54615	CJU101489	30492	66676	PAE204498
6370	42554	EFA202223	18432	54616	CJU101490	30493	66677	PAE204501
6371	42555	EFA201124	18433	54617	CJU101496	30494	66678	PAE204539
6372	42556	EFA201122	18434	54618	CJU101497	30495	66679	PAE204558
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6374	42558	EFA200290	18436	54620	CJU101499	30497	66681	PAE204560
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DNA SeqID	Protein SeqID	Gene LocusID	DNA SeqID	Protein SeqID	Gene LocusID	DNA SeqID	Protein SeqID	Gene LocusID
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6377	42561	EFA202136	18439	54623	CJU101502	30500	66684	PAE204565
6378	42562	EFA200195	18440	54624	CJU101503	30501	66685	PAE204566
6379	42563	EFA201951	18441	54625	CJU101513	30502	66686	PAE204567
6380	42564	EFA202174	18442	54626	CJU101517	30503	66687	PAE204586
6381	42565	EFA202221	18443	54627	CJU101518	30504	66688	PAE204593
6382	42566	EFA201401	18444	54628	CJU101521	30505	66689	PAE204599
6383	42567	EFA202115	18445	54629	CJU101523	30506	66690	PAE204600
6384	42568	EFA201506	18446	54630	CJU101528	30507	66691	PAE204602
6385	42569	EFA200829	18447	54631	CJU101530	30508	66692	PAE204603
6386	42570	EFA200400	18448	54632	CJU101531	30509	66693	PAE204604
6387	42571	EFA204122	18449	54633	CJU101536	30510	66694	PAE204607
6388	42572	EFA203071	18450	54634	CJU101537	30511	66695	PAE204623
6389	42573	EFA200247	18451	54635	CJU101540	30512	66696	PAE204625
6390	42574	EFA201826	18452	54636	CJU101544	30513	66697	PAE204643
6391	42575	EFA200381	18453	54637	CJU101547	30514	66698	PAE204653
6392	42576	EFA200382	18454	54638	CJU101548	30515	66699	PAE204659
6393	42577	EFA200797	18455	54639	CJU101550	30516	66700	PAE204660
6394	42578	EFA202211	18456	54640	CJU101551	30517	66701	PAE204661
6395	42579	EFA201645	18457	54641	CJU101558	30518	66702	PAE204663
6396	42580	EFA201646	18458	54642	CJU101563	30519	66703	PAE204667
6397	42581	EFA200366	18459	54643	CJU101565	30520	66704	PAE204670
6398	42582	EFA200731	18460	54644	CJU101577	30521	66705	PAE204684
6399	42583	EFA202608	18461	54645	CJU101578	30522	66706	PAE204690
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6404	42588	EFA200198	18466	54650	CJU101590	30527	66711	PAE204711
6405	42589	EFA200898	18467	54651	CJU101592	30528	66712	PAE204719
6406	42590	ECO100023	18468	54652	CJU101593	30529	66713	PAE204720
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6408	42592	ECO101256	18470	54654	CJU101595	30531	66715	PAE204724
6409	42593	ECO202228	18471	54655	CJU101596	30532	66716	PAE204725
6410	42594	ECO101324	18472	54656	CJU101597	30533	66717	PAE204728
6411	42595	ECO304472	18473	54657	CJU101598	30534	66718	PAE204729
6412	42596	ECO102309	18474	54658	CJU101599	30535	66719	PAE204734
6413	42597	ECO102636	18475	54659	CJU101600	30536	66720	PAE204736
6414	42598	ECO102557	18476	54660	CJU101601	30537	66721	PAE204737
6415	42599	ECO103884	18477	54661	CJU101602	30538	66722	PAE204738
6416	42600	ECO100148	18478	54662	CJU101603	30539	66723	PAE204741
6417	42601	ECO103240	18479	54663	CJU101604	30540	66724	PAE204745
6418	42602	ECO103241	18480	54664	CJU101605	30541	66725	PAE204746
6419	42603	ECO103394	18481	54665	CJU101606	30542	66726	PAE204747
6420	42604	ECO101485	18482	54666	CJU101607	30543	66727	PAE204752
6421	42605	ECO102255	18483	54667	CJU101608	30544	66728	PAE204754
6422	42606	ECO102144	18484	54668	CJU101609	30545	66729	PAE204755
6423	42607	ECO103911	18485	54669	CJU101610	30546	66730	PAE204757
6424	42608	ECO103264	18486	54670	CJU101611	30547	66731	PAE204764
6425	42609	ECO103265	18487	54671	CJU101612	30548	66732	PAE204765
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7316	43500	PAE201269	19378	55562	EBC101268	31439	67623	PPU101891
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8471	44655	ABA100614	20533	56717	ECO103275	32594	68778	PRT102444
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8475	44659	ABA100621	20537	56721	ECO103289	32598	68782	PRT102475
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8562	44746	ABA101163	20624	56808	ECO104239	32685	68869	PRT102997
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8582	44766	ABA101312	20644	56828	ECO202059	32705	68889	PRT103182
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10980	47164	BBU100494	23042	59226	KPN300279	35103	71287	SHA100112
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14644	50828	BPT100209	26706	62890	MCA100105	38767	74951	STM100933
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14742	50926	BPT100719	26804	62988	MCA100528	38865	75049	STM101688
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14821	51005	BPT100971	26883	63067	MCA100866	38944	75128	STM102429
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15457	51641	CAC100946	27519	63703	MLP100282	39580	75764	STY101925
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15509	51693	CAC101211	27571	63755	MLP100490	39632	75816	STY102219
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15512	51696	CAC101231	27574	63758	MLP100499	39635	75819	STY102227
15513	51697	CAC101250	27575	63759	MLP100500	39636	75820	STY102233
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15566	51750	CAC101568	27628	63812	MLP100700	39689	75873	STY102480
15567	51751	CAC101569	27629	63813	MLP100701	39690	75874	STY102481
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15714	51898	CAC102285	27776	63960	MLP101137	39837	76021	STY103176
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15720	51904	CAC102325	27782	63966	MLP101143	39843	76027	STY103211
15721	51905	CAC102328	27783	63967	MLP101144	39844	76028	STY103212
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16274	52458	CBO101553	28336	64520	MTU201262	40397	76581	TPA100720
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16349	52533	CBO102062	28411	64595	MTU201664	40472	76656	TPA100989
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16640	52824	CBO103826	28702	64886	MTU203412	40763	76947	VCH100040
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16645	52829	CBO103858	28707	64891	MTU203428	40768	76952	VCH100062
16646	52830	CBO103865	28708	64892	MTU203431	40769	76953	VCH100065
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16648	52832	CBO103872	28710	64894	MTU203456	40771	76955	VCH100083
16649	52833	CBO103873	28711	64895	MTU203460	40772	76956	VCH100105
16650	52834	CBO103874	28712	64896	MTU203462	40773	76957	VCH100108
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16658	52842	CBO103931	28720	64904	MTU203540	40781	76965	VCH100138
16659	52843	CBO103935	28721	64905	MTU203543	40782	76966	VCH100146
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16663	52847	CBO103952	28725	64909	MTU203556	40786	76970	VCH100162
16664	52848	CBO103956	28726	64910	MTU203558	40787	76971	VCH100165
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17546	53730	CDP100265	29608	65792	NME200732	41669	77853	YPS000732
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17548	53732	CDP100271	29610	65794	NME200734	41671	77855	YPS000760
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17552	53736	CDP100280	29614	65798	NME200757	41675	77859	YPS000771
17553	53737	CDP100282	29615	65799	NME200762	41676	77860	YPS000773
17554	53738	CDP100284	29616	65800	NME200764	41677	77861	YPS000774
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17556	53740	CDP100293	29618	65802	NME200772	41679	77863	YPS000779
17557	53741	CDP100296	29619	65803	NME200777	41680	77864	YPS000781
17558	53742	CDP100305	29620	65804	NME200783	41681	77865	YPS000784
17559	53743	CDP100306	29621	65805	NME200784	41682	77866	YPS000787
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17561	53745	CDP100309	29623	65807	NME200795	41684	77868	YPS000792
17562	53746	CDP100313	29624	65808	NME200800	41685	77869	YPS000797
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17573	53757	CDP100363	29635	65819	NME200849	41696	77880	YPS000846
17574	53758	CDP100365	29636	65820	NME200853	41697	77881	YPS000851
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17586	53770	CDP100399	29648	65832	NME200879	41709	77893	YPS000894
17587	53771	CDP100400	29649	65833	NME200881	41710	77894	YPS000900
17588	53772	CDP100404	29650	65834	NME200882	41711	77895	YPS000901
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17590	53774	CDP100409	29652	65836	NME200892	41713	77897	YPS000909
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17592	53776	CDP100414	29654	65838	NME200897	41715	77899	YPS000925
17593	53777	CDP100417	29655	65839	NME200899	41716	77900	YPS000930
17594	53778	CDP100418	29656	65840	NME200901	41717	77901	YPS000931
17595	53779	CDP100421	29657	65841	NME200903	41718	77902	YPS000933